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Original Communications

THE USE OF SULFAPYRIDINE IN PRIMARY PNEUMOCOCCIC PNEUMONIA AND IN PNEUMOCOCCIC PNEUMONIA ASSOCIATED WITH MEASLES

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IN MAY, 1938, Whitby[1] reported that 2-(p-aminobenzenesulfonamido) pyridine (sulfapyridine*), was able to protect mice against a number of types of pneumococci. Since Whitby's publication a number of authors have reported the use of this drug in the treatment of pneumonia. While no attempt will be made to review the literature on this subject, a few of the reports will be mentioned. Telling and Oliver[2] reported the successful treatment of a case of massive pneumonia due to Type 3 pneumococci. Evans and Gaisford[3] reported that the mortality rate among 100 adults with lobar pneumonia treated with sulfapyridine was only 8 per cent as compared with 27 per cent in 100 control cases. These authors stated in an addendum that they had also used the drug in 40 cases of pneumonia in children but did not give full results. Flippin and his associates[4] reported on the use of the drug in 100 adults with lobar pneumonia. Barnett and associates[5] described the use of sulfapyridine in the treatment of various pneumococcic infections in children. They reported 40 cases of pneumonia. All of their patients were proved by x-ray to have pulmonary consolidation, but no pneumococci were isolated from many of them. These authors concluded that their results were encouraging and recommended the use of the drug in pneumonia and other pneumococcic infections in children.

The present communication describes 71 cases of pneumococcic pneumonia in children treated with sulfapyridine.† Thirty-three with primary pneumonia were from the Harriet Lane Home. The thirty-

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*Sulfapyridine is the name which the Council on Pharmacy and Chemistry of the American Medical Association has recommended for 2-(p-aminobenzenesulfonamido) pyridine.

†The sulfapyridine used was obtained through Dr. Perrin Long by courtesy of Merck and Company, Inc., Rahway, N. J., and Calco Chemical Company, Inc., Bound Brook, N. J.

eight remaining patients with pneumonia associated with measles were treated at the Sydenham Hospital. In each instance definite pulmonary consolidation was demonstrated by x-ray, and pneumococci which were identified by type-specific sera were obtained from the nasopharynx. No patients who fulfilled these requirements were excluded from this study.

ISOLATION OF PNEUMOCOCCI

It is very difficult to obtain pneumococci for typing from children. Either sputum is not produced, or it is swallowed before it can be collected. In our experience throat cultures have not been entirely satisfactory. Pneumococci obtained in this manner have frequently been of a different type from those obtained from blood, empyema fluid, and pus from the middle ear. We have had no experience with lung punctures as a method for obtaining pneumococci.

Following the recommendation of Dr. Hattie Alexander,[7] we have employed cultures from the nasopharynx to isolate pneumococci from the patients comprising this study. We cannot be certain that the pneumococci found in the nasopharynx of patients with pneumonia are the organisms causing the disease, but in our experience during the past two years pneumococci obtained by this method have almost always been of the same type as those cultured from blood, empyema fluid, pus from the middle ear, and cerebrospinal fluid. This leads us to believe that pneumococci obtained from the nasopharynx are of greater etiological significance than those isolated from the throat.

The following technique is employed: A swab consisting of a small piece of cotton attached to the end of a flexible copper wire is inserted through the nose into the nasopharynx. The swab is then placed into 1 to 4 c.c. of ascitic fluid or blood broth and incubated at 37° C. for four to twelve hours. Pneumococci grow rapidly during this period. Part of the fluid is used for typing directly by the Neufeld-Sabin technique while 0.5 c.c. of the remainder is injected intra-abdominally into an Albino Swiss mouse. After eight to twelve hours a smear of fluid from the peritoneal cavity is made. If organisms which resemble pneumococci morphologically are seen, an attempt is made to agglutinate them by type-specific sera or to produce capsular swelling by the Neufeld-Sabin reaction. The types determined by the Neufeld-Sabin reaction and by agglutination have been identical in almost every instance.

TYPES OF PNEUMOCOCCI ISOLATED

In the Harriet Lane patients, all of whom had primary pneumonia, Type 14 was the organism most frequently isolated from the nasopharynx in the younger age group, and Type 1 in the older age group. This is illustrated in Table I. Type 14 was obtained twelve times from children under the age of 2 years and twice from patients over that age.

Type 1 was seen once under the age of 2 years and eight times over that age. The following types, showing no special grouping according to age, were also obtained:

Type 3	twice	Type 11	twice
4	twice	18	twice
6	3 times	19	3 times
7	once	29	once

In four cases two types of pneumococci were found, and in one case three types.

In the cases of pneumonia associated with measles, Type 14 was the organism most frequently isolated; it was found eleven times. Many other types, however, were also obtained.

Type 2	twice	Type 15	twice
3	once	16	once
4	twice	17	once
6	twice	18	twice
8	once	19	6 times
11	twice	23	3 times
		29	twice

Pneumococci were isolated from the blood in only 5 of the 71 patients. In each instance pneumococci of the same type were isolated from the nasopharynx. Pneumococci were cultured from the pus from the middle ear of 12 patients. Again in each case, pneumococci of the same type were isolated from the nasopharynx. These findings are in keeping with our previous experience regarding the close correlation between the type of pneumococci in the nasopharynx and those obtained from other sources.

X-RAY FINDINGS AND PHYSICAL SIGNS

X-ray films were taken soon after admission on all patients, and in almost all instances x-ray examinations were repeated at various intervals. In the patients at the Harriet Lane Home localized homogenous consolidation was demonstrated in every case. Of the 38 patients in the Sydenham Hospital, all of whom had pneumonia associated with measles, 21 also showed this localized homogenous consolidation, while the remaining 17 had a patchy, more or less diffuse type of infiltration.

The symptoms, physical signs, and leucocyte counts were those usually encountered in patients with pneumonia and will not be discussed here. The actual clinical condition of each patient is indicated in Tables I and II.

DOSAGE OF SULFAPYRIDINE

All the patients in this study received sulfapyridine by mouth. The dose varied between 1.2 gm. and 6.0 gm. in twenty-four hours,

depending upon the age of the child. The dosage employed is similar to that used by Barnett and co-workers.[5] The drug was given every six hours. In many instances the total twenty-four-hour dose was given at once on admission. The amount of the drug given in each case is noted in Tables I and II. In most cases the drug was continued until the temperature had been normal from five to eight days. It was continued for a longer period when otitis media or infected pleural fluid was present. On the other hand, on a few occasions it was stopped because of unfavorable reactions.

The concentration of free sulfapyridine was determined by a modification of Marshall's method for sulfanilamide.[6] These values varied over a wide range as can be seen in Tables I and II.

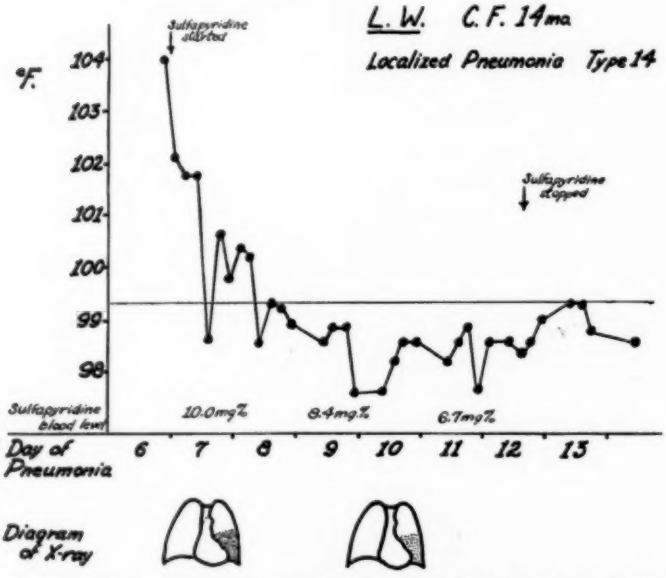

Chart 1.—Severely ill patient. Blood culture positive for Type 14 pneumococcus on admission and sterile on day after sulfapyridine was started. Sulfapyridine dosage, 2.4 gm. daily. Clinical improvement accompanied drop in temperature.

CLINICAL COURSE FOLLOWING SULFAPYRIDINE

Twelve of the patients were under 1 year; twenty-four were between the ages of 1 and 2 years; twenty were between the ages of 2 and 5 years; and fifteen were between the ages of 5 and 9 years. The clinical course following sulfapyridine was very similar in all age groups.

All the patients from the Harriet Lane Home had primary pneumonia. Many of the patients with primary pneumonia entered the hospital after they had been ill as long as five or six days. It should be noted that in these patients, as well as in those with pneumonia associated with measles, recovery took place in approximately the same time re-

gardless of the duration of the illness before treatment. Chart 1 illustrates the fall in temperature following sulfapyridine in an infant admitted on the sixth day of primary pneumonia; Type 14 pneumococci were isolated from the nasopharynx and the blood stream. Chart 2 is a similar record of a twenty-three-month-old infant who was only moderately ill but who was in the first day of the disease on admission. Chart 3 is a record of a 5-year-old white girl with Type 1 pneumonia, whose temperature became normal and who appeared well forty-eight hours after sulfapyridine was started.

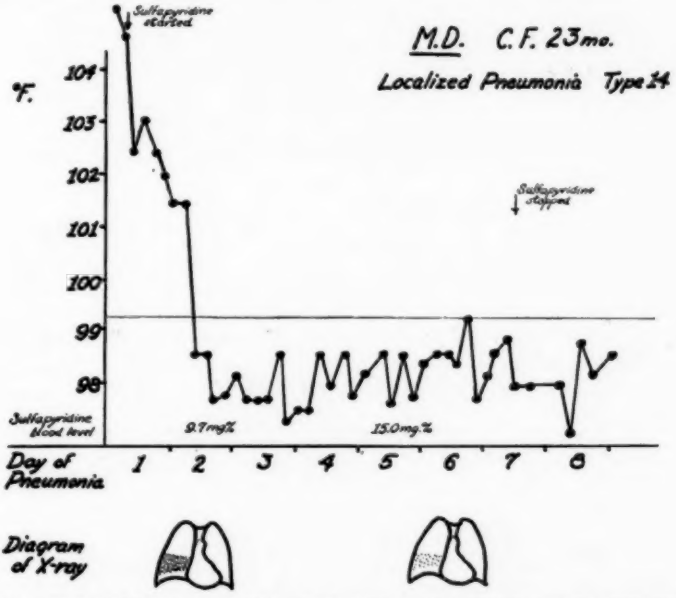

Chart 2.—Moderately ill patient with sterile blood culture whose general improvement paralleled the drop in temperature. Sulfapyridine dosage, 2.4 gm. daily.

The clinical improvement and fall in temperature following sulfapyridine occurred quite as strikingly in the patients with pneumonia associated with measles as in the cases of primary pneumonia. This is illustrated in Chart 4, which is the record of a critically ill 2-year-old infant with diffuse bilateral pneumonia associated with measles. Temperature fell abruptly after sulfapyridine, and the patient appeared greatly improved within twenty-four hours. Type 6 pneumococci were isolated from the nasopharynx and many beta hemolytic streptococci from the throat.

As can be seen in Tables I and II, which summarize the data on all patients, the temperature became normal within thirty-six hours or forty-eight hours after sulfapyridine was begun in almost every case. Charts 5 and 6, prepared by Dr. Thurber Fales, record the temperatures at

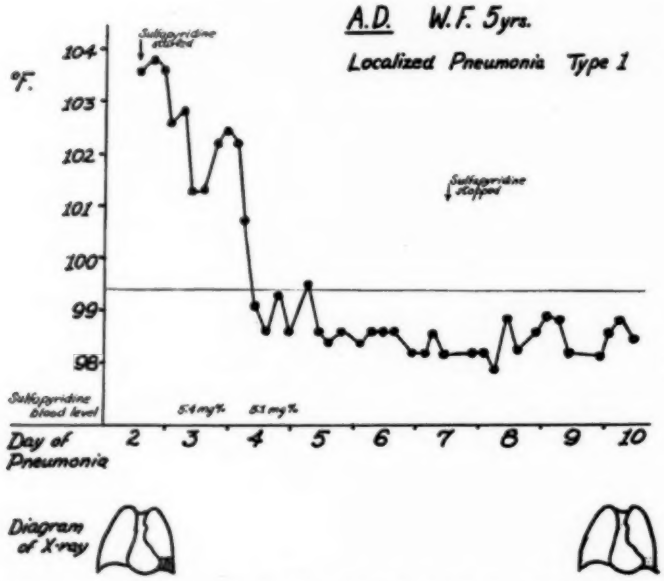

Chart 3.—Moderately ill patient with sterile blood culture. Marked improvement accompanied fall in temperature. Sulfapyridine dosage, 0.9 gm. immediately and 2.4 gm. daily.

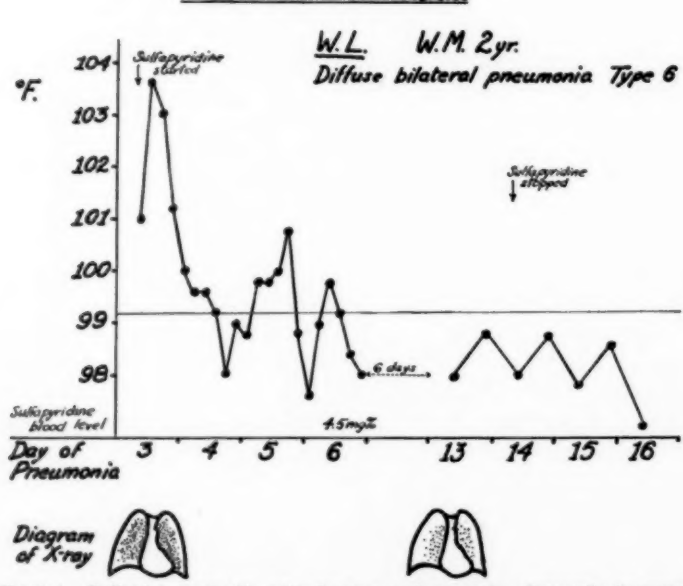

Chart 4.—Patient severely ill, with dyspnea and cyanosis. Dramatic improvement in twenty-four hours. Dyspnea continued for forty-eight hours after temperature became normal. Sulfapyridine dosage, 2.5 gm. immediately and 2.0 gm. daily.

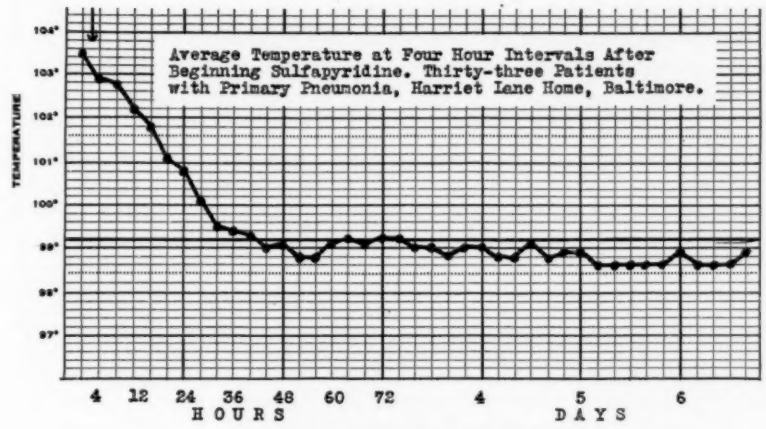

Fig. 5.

four-hour intervals after the beginning of sulfapyridine therapy. Comparison of these charts shows that the average fall in temperature in the two groups was quite similar. The average temperature became normal in patients with primary pneumonia in forty hours, while the average temperature curve in the measles pneumonia cases reached the normal line in about thirty hours. The slope of the curve in the measles patients is somewhat more abrupt, but this may be due to the fact that all patients with measles pneumonia received a large initial dose, while most of the children with primary pneumonia did not receive such a dose. It is realized, of course, that curves made up of average values

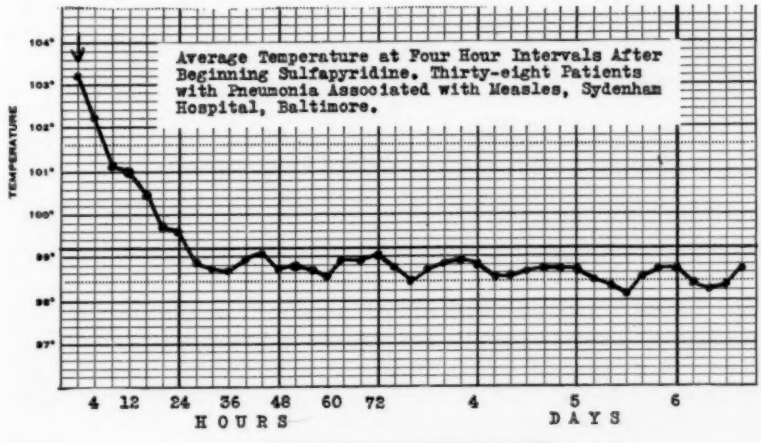

Fig. 6.

may have little meaning, but the average values plotted on Charts 5 and 6 are very close to the median values. This indicates that there were as many temperatures below the average figures recorded as there were above them.

Coincident with the fall in temperature most of the patients showed great clinical improvement. However, a few of the children remained dyspneic and appeared ill for one or two days longer. Accurate evaluation of clinical improvement is difficult, but we are of the opinion that the course of the pneumonia was shortened by the use of sulfapyridine. This was especially striking in those patients with diffuse pneumonia associated with measles. Pneumonia of this type usually produces an illness of at least one or two weeks, but none of the patients receiving sulfapyridine remained ill more than 48 hours.

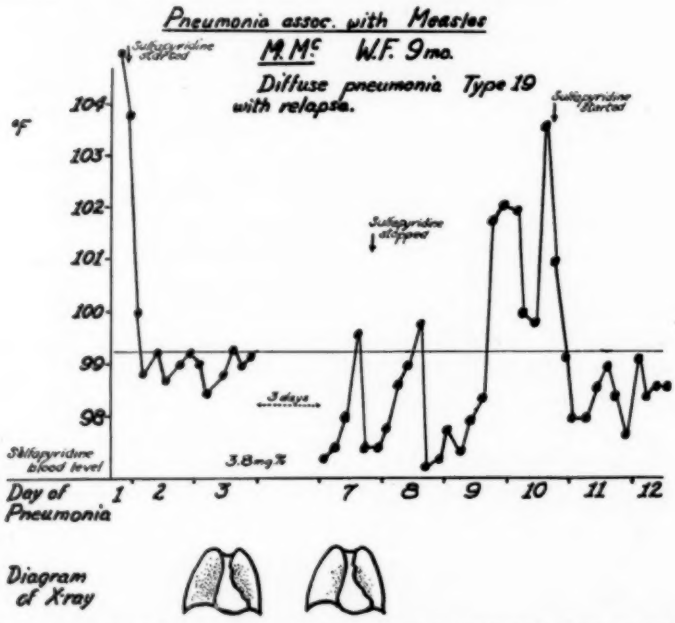

Chart 7.—Moderately ill patient. Much improved in forty-eight hours on sulfapyridine dosage of 2.0 gm. immediately and 1.2 gm. daily. Drug stopped on seventh day because of moderate neutropenia. Thirty-six hours later temperature rose and patient again appeared sick. Responded to sulfapyridine without recurrence of neutropenia. Recovery uneventful.

The physical findings in the lungs usually persisted after the temperature had become normal. This was true also of the shadows seen on x-ray. It is our impression that the pneumonic consolidation did not disappear more rapidly in our patients than is usually the case in children who spontaneously recover from pneumonia.

On two occasions the withdrawal of the drug was followed by a sharp rise in temperature and a return of symptoms. In both cases the symp-

toms disappeared, and the temperature became normal very soon after the drug was begun again. Chart 7 illustrates a case in which recurrence of symptoms and an abrupt rise in temperature followed the early withdrawal of sulfapyridine. The temperature fell and the symptoms disappeared promptly when the drug was again administered.

Beta hemolytic streptococci (Lancefield, Group A) were cultured in large numbers from the throats of some of the patients in the measles group. These children recovered as promptly as those in whom very few or no streptococci were found.

All 71 patients in this study recovered.

COMPLICATIONS

Purulent otitis media occurred three times in the group of patients with primary pneumonia. Two of these had otitis media on admission. The other developed this complication after sulfapyridine was stopped. In two of these cases the pneumococcus isolated was of the same type as that obtained from the nasopharynx. Purulent otitis media was present in fifteen patients of the measles group on admission, while one patient developed this condition after sulfapyridine was stopped. Pus from the middle ear of fourteen of these patients was cultured, and the pneumococci of the same type as those in the nasopharynx were obtained in ten, while no pneumococci were isolated in the other four.

None of the patients in this study developed empyema after the institution of sulfapyridine therapy. However, one patient (E. M.), a 22-month-old colored infant, entered the hospital with empyema, pneumonia, and bacteremia due to Type 1 pneumococci. In the first six weeks after the development of empyema the child became febrile on several occasions after withdrawal of sulfapyridine. During this period a number of nasopharyngeal cultures yielded Type 1 pneumococci. X-ray films showed thickening of the pleura but no free fluid, and no pus could be obtained by thoracentesis. At present, eight weeks after admission, the child is receiving no sulfapyridine, is afebrile and appears entirely well.

PERSISTENCE OF PNEUMOCOCCI IN NASOPHARYNX

In the measles group an attempt was made to determine the effect of sulfapyridine on the presence of pneumococci in the nasopharynx. Cultures were taken one or more times from 25 patients while they were receiving the drug. In 6 of these were pneumococci isolated. Cultures were also made on 23 of these patients, at least two days after sulfapyridine was stopped. In 12 of these pneumococci were found. It seems evident that patients recovering from pneumonia after sulfapyridine therapy may still harbor pneumococci in the nasopharynx. It is possible that this may have some bearing upon the occurrence of relapses. In our series 4 children developed a second attack of pneumonia within two weeks after sulfapyridine had been discontinued. In 3 of these patients the relapse was apparently caused by the same organism which

was responsible for the first attack. In all but one of these children the pneumonia occurred in the same place during both episodes.

We have encountered three instances in which pneumococci from one patient were transferred to an adjacent child whose original pneumococci had disappeared. This transfer was followed by an upper respiratory infection in these children who were not at that time receiving sulfapyridine. Chart 8 summarizes the findings in one of these patients who experienced such a superimposed infection.

UNTOWARD EFFECTS

Mild anorexia occurred in many of the patients, and nausea and vomiting in a few. Seldom were these symptoms sufficiently severe to necessitate stopping the drug.

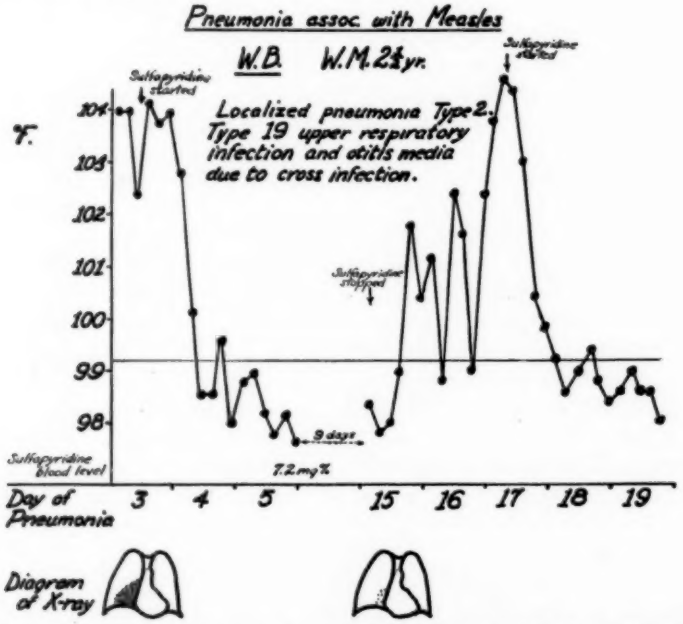

Chart 8.—Moderately sick patient. Prompt improvement following sulfapyridine which was discontinued on the fifteenth day. Forty-eight hours later temperature rose to 104.8° F. due to sinusitis and otitis caused by Type 19 pneumococcus. Myringotomy was done and sulfapyridine begun. Temperature returned to normal. Probably cross infection from patient in next bed (J. H.) who had Type 19 pneumonia. Sulfapyridine dosage, 1.5 gm. immediately and 2.0 gm. daily.

Granulocytopenia occurred in a mild form 5 times and in a more severe form once. All these patients recovered promptly when the drug was withdrawn. In one of these children the granulocytopenia occurred while a second course of the drug was being given. In two of the other patients sulfapyridine was given again after recovery, without appreciable decrease in granulocytes. Frequent hemoglobin determinations were made, but significant changes were not noted.

Gross hematuria was seen in two patients in this study and has been noted by us in two other cases receiving sulfapyridine by mouth. In all instances the urine became clear within a few days after the drug was stopped. Hematuria was also noted in one patient who had received sulfapyridine by mouth and the sodium salt of sulfapyridine intravenously. Addis counts and kidney function tests have revealed no permanent renal damage following the hematuria.

Cyanosis has been seen only rarely, and we are certain that in only one case was it caused by the drug and not by the pneumonia.

A morbilliform rash on the face, trunk, and extremities, accompanied by fever and vomiting, was observed in one case. These symptoms disappeared within eight hours after withdrawal of sulfapyridine.

It is possible that these reactions might be avoided by the use of smaller doses. Further experience may show that the dosage used by us is larger than that necessary to produce effective therapeutic results.

COMMENT

Type-specific horse and rabbit sera have been used in the treatment of pneumococcic pneumonia in children on the wards of the Harriet Lane Home. The results have been good and in some cases striking. This form of therapy has, however, certain disadvantages when used on children. The type of pneumococcus must be determined before serum can be given, and difficulties in typing may cause serious delay in starting therapy. Sometimes more than one type of pneumococcus is found in a patient and it is impossible to be certain which organism is causing the pneumonia. Serious serum reactions are infrequent, but they do occur occasionally despite all precautions. The child who receives serum may become sensitive to the serum of the animal used. Many of our patients are too young to be cooperative and are greatly disturbed by serum administration. The cost of treating a patient with serum is much greater than it is with sulfapyridine. In our experience the mortality rate for acute primary pneumonia in infants and children is very low, and the use of a specific form of therapy which has disadvantages, although not great ones, may be questionable.

However, pneumonia in children is sufficiently serious to justify the search for some effective therapeutic agent. This is particularly true in pneumonia accompanying measles and pertussis. Our experience leads us to believe that sulfapyridine is effective in both primary pneumonia and in the pneumonia associated with measles. In nearly every case the administration of sulfapyridine was followed within forty-eight hours by a fall in temperature to normal and by prompt improvement, and none of the 71 patients died.

It was our impression that these patients were not so severely ill as those seen in previous years. This impression is substantiated by the fact that positive blood cultures were obtained in only 3 cases in the Harriet Lane group. However, 5 of these patients were severely ill

TABLE I

HARRIET LANE HOME (PRIMARY PNEUMONIA)

PATIENT	DAY OF PNEUMONIA	TEMP. (R) REPRESENTS AVERAGE OF 1ST 12 HOURS	GENERAL CONDITION	CONSOLIDATION (X-RAY)	PNEUMOCOCCUS TYPE		W.B.C.	SULFAPYRIDINE		TIME REQUIRED FOR TEMP. TO REACH NORMAL	COURSE
					NASOPHARYNX	BLOOD		DOSE (GRAM)	BLOOD LEVEL (MG. %)		
E.M. 5 mo. C.M.	2nd	101.3 F. (38.5 C.)	M. I.*	Infiltration in both U.L.	14	Sterile	6,000 (on adm.) 9,000 (3rd day)	1.2 stat. 0.6 q. 6 h. for 7 days	14.0	48 hours	The noticeable clinical improvement at the time the temperature dropped became more marked during the next 2 days.
R.B. 6 mo. C.M.	7th	104.7 F. (40.4 C.)	M. I.	R.L.L.	14	Sterile	34,000 (on adm.) 23,250 (2nd day) 10,300 (4th day)	0.6 q. 6 h. for 11 days	5.0–12.6	4 days	Sharp improvement at the time the temperature became normal was accompanied by marked clearing by x-ray.
S.W.J. 7 mo. Y.M.	2nd	105.0 F. (40.6 C.)	M. I.	L.L.L.	4	Sterile	24,600 (on adm.) 13,450 (2nd day) 10,450 (4th day)	0.6 q. 6 h. for 6 days	9.1–10.2	30 hours	Great clinical improvement followed closely upon the drop in temperature. Consolidation had disappeared by x-ray after 4 days.
H.H. 9 mo. C.M.	2nd	103.2 F. (39.6 C.)	M. I.	R.U.L.	14	Sterile	26,600 (on adm.) 20,100 (2nd day) 14,200 (3rd day)	0.3 q. 6 h. for 3 days	6.3	30 hours	Definite improvement in general condition occurred at time of drop in temperature. No subsequent x-rays.
R.S. 9 mo. C.M.	4th	104.0 F. (40.0 C.)	M. I.	L.U.L. (partial)	19	Sterile	10,700 (on adm.) 6,400 (2nd day)	0.6 q. 6 h. for 6 days	7.8–12.6	48 hours	Clinical improvement was not impressive until 3 days after the fall in temperature, but x-ray clearing was apparent in 2 days.
E.J. 10 mo. C.M.	7th	102.2 F. (39.0 C.)	S. I.†	R.U.L.	14	Sterile	34,000 (on adm.) 57,000 (2nd day) 10,000 (6th day)	0.3 q. 4 h. for 6 days	4.5	4 days	Sulfapyridine was not given until the 4th day in the hospital. Clinical improvement and x-ray clearing were gradual. 12 days after the drug was stopped, it was given again because of otitis media. The W.B.C. dropped to 4,200 with 8% granulocytes, but returned quickly to normal after the drug was discontinued.

TABLE I—CONT'D

E.S. 10 mo. C.M.	2nd	102.9 F. (39.4 C.)	M. I.	R.U.L.	14 and 19	Sterile	32,000 (on adm.) 11,600 (3rd day) 7,650 (5th day)	0.3 q. 6 h. for 6 days	4.2– 9.0	36 hours	Great clinical improvement with disappearance of physical signs in chest followed the drop in temperature, but no further x-rays were taken. Two weeks after the drug was stopped the child returned with a recurrence of pneumonia at the same site with the same organisms. Sulfapyridine dosage and course essentially the same. There was gradual x-ray clearing of the consolidation over a 9-day period.
M.W. 12 mo. C.F.	4th	104.0 F. (40.0 C.)	S. I.	L.L.L. with small amt. of fluid	18	18 (13 cols.)	18,500 (on adm.) 14,000 (2nd day) 25,000 (3rd day)	0.6 q. 6 h. for 2 weeks	15.2	1 week	The temperature showed a precipitate drop to normal in the 1st 24 hours but rose again and ranged from 38-40° C. for 1 week, after which it became essentially normal. Blood culture was sterile 2 days after treatment was started. Thoracentesis produced 1 c.c. of sterile fluid. There was gradual clearing on x-ray over period of 1 month.
J.E. 12 mo. C.M.	2nd	102.9 F. (39.4 C.)	M. I.	Patches in both lungs	14	Sterile	66,000 (on adm.) 16,700 (3rd day)	0.6 q. 6 h. for 6 days	–	30 hours	Rapid clinical improvement with fall of temperature to normal.
L.C. 13 mo. C.F.	2nd	102.2 F. (39.0 C.)	M. I.	R.L.L.	18	–	28,000 (on adm.) 13,600 (3rd day) 10,900 (4th day)	0.3 q. 6 h. for 6 days	4.5– 7.3	48 hours	General improvement accompanied fall of temperature to normal, and there was slight clearing of consolidation by x-ray in 3 days.
L.W. 14 mo. C.F.	6th	102.5 F. (39.2 C.)	S. I.	L.L.L.	14	14	66,000 (on adm.) 35,600 (2nd day) 24,300 (3rd day) 22,650 (4th day)	0.6 q. 6 h. for 6 days	4.4– 10.0	36 hours	The blood culture was sterile the day after treatment was begun, and clinical improvement followed the fall in temperature. X-ray showed considerable clearing in 3 days. A week after discharge pneumonia recurred at the same site. Again prompt improvement after sulfapyridine.

TABLE I—CONT'D

PATIENT	DAY OF PNEUMONIA	TEMP. (R) REPRESENTS AVERAGE OF 1ST 12 HOURS	GENERAL CONDITION	CONSOLIDATION (X-RAY)	PNEUMOCOCCUS TYPE		W.B.C.	SULFAPYRIDINE		TIME REQUIRED FOR TEMP. TO REACH NORMAL	COURSE
					NASOPHARYNX	BLOOD		DOSE (GRAM)	BLOOD LEVEL (MG. %)		
S.H. 16 mo. C.F.	1st	103.2 F. (39.6 C.)	M. I.	L.L.L.	6, 14, 29	Sterile	25,560 (on adm.) 10,000 (3rd day)	0.5 q. 6 h. for 2 days	–	24 hours	Child was clinically well after 24 hours.
A.G. 19 mo. W.M.	4th	103.6 F. (39.8 C.)	S. I.	R.U.L. & R.L.L. (sm. area cons. both)	14	Sterile	39,000 (on adm.) 34,700 (2nd day) 14,400 (4th day)	0.3 q. 6 h. for 7 days	3.5	30 hours	X-ray showed signs of fluid on right. 20 c.c. of thin, bloody, sterile fluid removed. Marked symptomatic improvement with drop in temperature. X-ray revealed definite clearing in 3 days and complete resolution in 8 days.
C.A. 20 mo. W.F.	2nd	102.2 F. (39.0 C.)	M. I.	L.L.L. (partial)	3 and 6	Sterile	54,000 (on adm.) 32,000 (2nd day) 28,800 (3rd day)	0.6 q. 6 h. for 6 days	8.3	24 hours	Child continued to look ill and had extreme anorexia for 2 days after temperature was normal, followed by uneventful recovery. X-ray revealed almost complete clearing of consolidation in 4 days.
E.M. 22 mo. C.F.	3rd	103.2 F. (39.6 C.)	M. I.	L.L.L. (fluid in periphery)	1 and 11	1	34,000 (on adm.) 24,400 (2nd day) 20,200 (3rd day)	0.5 q. 6 h. for 10 days	4.2–10.9	1 week	Pneumonia, empyema, positive blood culture on admission. Required 8 weeks for complete recovery (see text).
R.D. 22 mo. W.M.	4th	103.2 F. (39.6 C.)	M. I.	R.M.L.	14	–	21,000 (on adm.) 13,000 (4th day)	0.9 q. 6 h. for 6 days	10.3	36 hours	Greatly improved after cessation of fever. There was bilateral otitis media, and Type 14 pneumococcus was cultured from the pus. The otitis media persisted for about 2 weeks after the drug was stopped.

TABLE I—CONT'D

M.D. 23 mo. C.F.	1st	104.0 F. (40.0 C.)	M. I.	R.M.L.	14	Sterile	26,100 (on adm.) 20,400 (2nd day) 16,100 (5th day)	1.2 stat. 0.6 q. 6 h. for 6 days	9.7–15.0	32 hours	Much improved clinically at time temperature became normal. X-ray showed beginning clearing on 5th day.
R.H. 23 mo. C.M.	2nd	103.6 F. (39.8 C.)	M. I.	R.U.L.	14	Sterile	35,000 (on adm.) 31,800 (2nd day) 11,000 (3rd day)	0.3 q. 4 h. for 5 days	–	24 hours	General improvement coincided with fall in temperature. Considerable x-ray clearing in 4 days. Very slight residual clouding after 1 month.
M.D. 2 yr. C.F.	3rd.	103.6 F. (39.8 C.)	M. I.	L.L.L.	14	Sterile	38,000 (on adm.) 7,800 (3rd day)	2.0 stat. 1.0 q. 6 h.	11.8	30 hours	Pulse and respiration remained high and child continued to seem ill for 3 days following the fall in temperature. Thereafter recovery was uneventful.
M.S. 2 yr. C.F.	3rd	103.2 F. (39.6 C.)	M. I.	R.U.L.	19	Sterile	27,550 (on adm.) 20,300 (2nd day) 13,000 (3rd day)	0.6 q. 6 h. for 5 days	3.7–4.2	36 hours	Clinical improvement and disappearance of physical signs coincided with drop in temperature. X-ray clearing was complete by 7th day.
P.B. 2½ yr. C.M.	4th	104.0 F. (40.0 C.)	S. I.	L.L.L.	1 and 11	Sterile	15,750 (on adm.) 5,000 (3rd day)	0.9 stat. 0.6 q. 6 h. for 3 days	4.0	24 hours	Great improvement accompanied disappearance of fever. X-ray clearing in 7 days.
W.S. 2½ yr. C.M.	5th	104.0 F. (40.0 C.)	M. I.	R.L.L.	1	Sterile	23,920 (on adm.) 22,800 (3rd day) 11,000 (5th day)	0.6 q. 6 h. for 5 days	3.7–10.7	48 hours	Child was greatly improved and there was clearing by x-ray after 48 hours. X-ray clearing was complete after 7 days. When ready for discharge on the 10th day, the child developed a fresh respiratory infection with otitis media but without fever. Type 1 pneumococcus was recovered from the drainage from both ears. Ears were dry after 11 days of sulfapyridine therapy at the same dosage. Child discharged 5 days later and has remained well.

TABLE I—CONT'D

PATIENT	DAY OF PNEUMONIA	TEMP. (R) REPRESENTS AVERAGE OF 1ST 12 HOURS	GENERAL CONDITION	CONSOLIDATION (X-RAY)	PNEUMOCOCCUS TYPE		W.B.C.	SULFAPYRIDINE		TIME REQUIRED FOR TEMP. TO REACH NORMAL	COURSE
					NASOPHARYNX	BLOOD		DOSE (GRAM)	BLOOD LEVEL (MG. %)		
N.S. 2½ yr. C.F.	3rd	104.0 F. (40.0 C.)	M. I.	R.L.L.	14	Sterile	26,000 (on adm.) 23,850 (2nd day) 14,000 (3rd day) 8,000 (4th day)	0.6 q. 6 h. for 5 days	2.0–9.6	24 hours	Child appeared cured when temperature became normal. There was marked clearing on x-ray by the 4th day and complete clearing by 9th day.
C.W. 3½ yr. C.F.	2nd	102.9 F. (39.4 C.)	M. I.	R.L.L.	4	Sterile	29,000 (on adm.) 28,500 (2nd day) 13,900 (3rd day) 9,500 (4th day)	0.6 q. 6 h. for 3 days	5.7–8.6	28 hours	Child appeared cured following disappearance of fever. Physical signs of consolidation were disappearing by 3rd day. Complete x-ray clearing by 10th day.
A.D. 5 yr. W.F.	2nd	103.1 F. (39.5 C.)	M. I.	L.L.L. (large patch)	1	Sterile	29,450 (on adm.) 25,700 (2nd day) 11,500 (3rd day)	0.6 q. 6 h. for 4 days	5.1–5.4	48 hours	Marked improvement accompanied fall of temperature to normal. Consolidation was almost completely resolved by x-ray on the 6th day.
M.S. 5 yr. C.M.	10th	101.3 F. (38.5 C.)	M. I.	R.L.L. (patch)	1	Sterile	35,800 (on adm.) 24,600 (2nd day) 12,400 (3rd day)	3.0 stat. 1.0 q. 4 h. for 2 days	7.8	12 hours	Admission temperature of 40.6° C. fell to normal in 12 hours. Child's general improvement was slow and gradual. X-ray clearing complete in 7 days.
T.W. 5 yr. C.F.	2nd	103.6 F. (39.8 C.)	M. I.	Patch adjacent to right heart border	6	Sterile	21,040 (on adm.) 25,900 (2nd day) 20,650 (3rd day) 10,800 (4th day)	3.0 stat. 1.0 q. 6 h. for 3 days	–	36 hours	Continued to look ill for 3 days after the temperature became normal, but thereafter improved rapidly. Albuminuria and hematuria without increased blood pressure developed on the 3rd day and decreased rapidly on stopping the drug. The urine was clear 4 days later.

TABLE I—CONT'D

H.C. 6 yr. C.M.	2nd	104.0 F. (40.0 C.)	M. I.	R.U.L.	7	Sterile	40,500 (on adm.) 19,360 (3rd day) 9,600 (7th day)	Given irreg. (because vomiting) for 3 days	7.3	36 hours	Patient was asthmatic, and wheezing continued in spite of clinical improvement after the fall in temperature. There was x-ray clearing on the 6th day when child had to be transferred to another hospital because of measles.
D.W. 6 yr. W.M.	3rd	103.1 F. (39.5 C.)	M. I.	L.L.L.	1	Sterile	34,200 (on adm.) 15,560 (2nd day) 7,450 (3rd day)	0.6 q. 6 h. for 6 days	4.6	28 hours	Striking improvement with fall of temperature to normal. Physical signs disappeared after the 5th day. Clearing on x-ray had not begun on 3rd day; no further plates.
P.S. 7 yr. C.M.	7th	101.1 F. (38.4 C.)	M. I.	L.U.L.	3	Sterile	28,800 (on adm.) 35,000 (2nd day) 15,300 (3rd day) 7,200 (4th day)	3.0 stat. 1.5 q. 6 h. for 6 days	5.2–14.1	24 hours	General improvement was gradual. Chest was entirely clear in 7 days.
A.B. 8 yr. W.F.	2nd	104.0 F. (40.0 C.)	M. I.	R.U.L.	1	Sterile	33,650 (on adm.) 14,350 (2nd day) 5,450 (3rd day)	0.9 q. 6 h. for 5 days	4.6	36 hours	Marked improvement accompanied return of temperature to normal. No x-ray clearing by 3rd day, but was beginning on 6th day and almost complete by 10th day.
P.E. 8 yr. W.M.	4th	101.4 F. (38.6 C.)	M. I.	L.U.L. (patch)	1	Sterile	19,200 (on adm.) 16,200 (2nd day) 10,400 (3rd day) 5,900 (4th day)	2.5 stat. 1.5 q. 6 h. for 6 days	–	30 hours	Much improved after drop in temperature. No change in consolidation after 6 days, but definite clearing by x-ray on the 12th day.
H.D. 9 yr. W.M.	1st	102.5 F. (39.2 C.)	M. I.	Mid-portion of right lung	1	Sterile	40,200 (on adm.) 51,600 (2nd day) 36,000 (3rd day)	2.5 stat. 1.5 q. 6 h. for 2 days	12.5	36 hours	Child greatly improved after temperature became normal. Consolidation almost gone in 2 days. Vomiting occurred repeatedly during the 2 days the drug was given and ceased at once when sulfapyridine was withdrawn.

*M. I., moderately ill.
†S. I., severely ill.

TABLE

SYDENHAM HOSPITAL (PNEUMONIA

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
T.G. 4 mo. W.M.	1	Severely ill. Dyspnea. T. 102.2.	1.5 gm. stat. 0.25 gm. q. 6 h.	60	Admission: Bilateral patchy pneumonia. 12 days later normal.	11	11	11
M.M. 6 mo. W.F.	2	Moderately ill. Moderate dyspnea. Otitis media. T. 104	2.0 gm. stat. 0.5 gm. q. 6 h.	28	Admission: Patchy diffuse pneumonia. 4 days later clearing	14	Not done	Not done
M.McK. 9 mo. W.F.	1	Critically ill. Marked dyspnea Otitis media. T. 105	2.0 gm. stat. 0.3 gm. q. 6 h.	16	Admission: Patchy pneumonia. 10 days later normal.	19	Neg.	19
N.H. 11 mo. W.M.	1	Critically ill. Cyanosis. Great dyspnea. Otitis media. T. 102.8	2.0 gm. stat. 0.5 gm. q. 6 h.	72	Admission: Diffuse pneumonia (interstitial). 1 month later unresolved	23	Not done	Neg.
H.R. 11 mo. W.M.	3	Severely ill. Moderate dyspnea. T. 103.4	2.0 gm. stat. 0.25 gm. q. 6 h. 0.5 gm. q. 6 h.	20 (see summary)	Admission: Homogenous density, right lower lobe. 9 days later normal	6	Neg.	Neg.
J.W. 12 mo. C.M.	1	Moderately ill. T. 102	2.0 gm. stat. 0.5 gm. q. 6 h.	16	Admission: Diffuse patchy pneumonia. 3 days later clearing	29	Neg.	Not done
J.O. 13 mo. W.F.	3	Severely ill. Moderate dyspnea. Cyanosis. T. 102.8	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Homogenous density, right upper lobe. 8 days later normal	14	Not done	Not done

II

ASSOCIATED WITH MEASLES)

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	--	Not done	8.5	None	Remained ill for 36 hours. Improvement thereafter fairly rapid although temperature did not become normal until 60 hours after sulfapyridine. Uneventful convalescence thereafter.
Sterile	14	Many	11.5	None	Both type 14 pneumo. and beta strept. isolated, prompt recovery within 24 hours after sulfapyridine. Drainage from middle ear ceased 2 days after sulfapyridine.
Sterile	19	Few	3.8	Granulocytopenia	Temperature normal 12 hours after sulfapyridine, and remained so 9 days when drug stopped because of granulocytopenia. 2nd rise in temperature followed; again reduced to normal by drug. No recurrence of granulocytopenia.
Sterile	Neg.	Neg.	10.0	None	Improvement slow. Temperature normal 72 hours after sulfapyridine. Convalescence uneventful. X-ray clearing at time of discharge. Re-admitted 2 weeks later with temperature of 103.8 and recurrence of symptoms. Unresolved pneumonia still present. Type 2 pneumococcus isolated from nasopharynx. Temperature became normal 20 hours after sulfapyridine. Normal convalescence.
Sterile	--	Neg.	5.5	None	Definite and rapid improvement in general condition within 24 hours. However, temperature rose gradually after initial fall, probably due to small dose. Increase in dosage followed by prompt fall in temperature within 18 hours.
Sterile	--	Neg.	10.6	None	Appeared entirely well within 24 hours after sulfapyridine. Uneventful convalescence.
Sterile	--	Neg.	3.9	None	Within 24 hours after sulfapyridine child sitting up in bed entirely well.

TABLE

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
G.S. 13 mo. W.M.	3	Moderately ill. Moderate dyspnea. T. 104	1.0 gm. stat. 0.3 gm. q. 6 h.	24	Admission: Homogenous density, right upper lobe. 10 days later normal.	3	Neg.	3
S.M. 13 mo. W.F.	2	Moderately ill. Moderate dyspnea. T. 105	2.0 gm. stat. 0.5 gm. q. 6 h.	28	Admission: Homogenous density, left lower lobe. 8 days later normal.	14	Neg.	Neg.
A.W. 14 mo. W.M.	1	Moderately ill. T. 104	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Homogenous density, right lower lobe. 4 days later normal.	23	Neg.	Neg. for 23. Pos. for 14. (See text)
I.R. 16 mo. C.F.	2	Moderately ill. Otitis media. T. 102	2.5 gm. stat. 0.5 gm. q. 6 h.	22	Admission: Homogenous density, right upper lobe. 12 days later normal.	19	Neg.	Neg.
A.P. 18 mo. W.F.	1	Severely ill. Lethargic. Dyspnea. T. 103.4	2.0 gm. stat. 0.5 gm. q. 6 h.	30	Admission: Patchy pneumonia, left lung. 13 days later normal	14	14	14
C.K. 18 mo. W.F.	1	Critically ill. Moderate dyspnea. T. 105	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Homogenous density, right upper lobe. 7 days later normal.	14	Neg.	14 (still 1 mo. after admission)
E.F. 13 mo. W.M.	2	Moderately ill. Slight dyspnea. T. 102.8	2.0 gm. stat. 0.5 gm. q. 6 h.	32	Admission: Homogenous density, left lower lobe. 7 days later normal.	11	Neg.	Not done

II—CONT'D

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	--	Few	2.3	None	Within 24 hours after sulfapyridine child appeared well and temperature normal. Uneventful convalescence.
Not done	--	Neg.	Not done	Granulocytopenia	Following complete recovery from primary pneumonia of right upper lobe (Type 14), treated with sulfapyridine, patient contracted measles. Coincident with rash primary pneumonia of left lower lobe (Type 14), developed. Again prompt recovery from sulfapyridine.
Sterile	--	Very many	11.4	None	Mild pneumonia due to Type 23 pneumococcus. Prompt recovery and uneventful convalescence. After sulfapyridine stopped Type 14 pneumococcus cultured from nasopharynx. This organism had caused pneumonia of patient (A. P.) in next bed.
Sterile	Not done	Very large number	9.6	None	Rapid improvement and uneventful convalescence following sulfapyridine.
Sterile	--	Neg.	10.7	None	Child's temperature normal, sitting up in bed, alert and well 24 hours after sulfapyridine.
Sterile	--	Neg.	5.7	Moderate granulocytopenia	Dramatic improvement 24 hours after sulfapyridine. Drug discontinued after 2 days, due to granulocytopenia. 13 days later sinusitis and cervical adenitis developed with temperature 105. No pneumonia on x-ray. Sulfapyridine begun again; temperature normal within 24 hours. Uneventful convalescence. No recurrence of granulocytopenia. Type 14 pneumococcus in nasopharynx 30 days after admission.
Sterile	--	Very many	6.8	None	Only moderately ill on admission. Effect of sulfapyridine difficult to estimate.

TABLE

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
G.R. 19 mo. W.M.	1	Severely ill. Moderate dyspnea. T. 103	2.0 gm. stat. 0.5 gm. q. 6 h.	16	Admission: Homogenous density, right upper lobe. 4 days later normal.	19	Not done	Not done
G.S. 20 mo. C.F.	1	Undernourished child. Moderately ill. Slight dyspnea. T. 102.4	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Bilateral patchy pneumonia. 8 days later normal.	17	Neg.	Neg.
E.F. 21 mo. W.F.	1	Severely ill. Cyanosis. Dyspnea. Otitis media. T. 103.6	1.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Diffuse patchy pneumonia. 7 days later clearing	23	Neg.	Not done
B.L.M. 22 mo. W.F.	2	Critically ill. Marked dyspnea. Otitis media. T. 104	2.0 gm. stat. 0.25 gm. q. 6 h.	24	Admission: Patchy pneumonia, right lung. 8 days later normal	16	Neg.	16
M.P. 2 yr. W.F.	1	Moderately ill. Otitis media. T. 103.6	2.5 gm. stat. 0.5 gm. q. 6 h.	16	Admission: Patchy pneumonia, right lung. 10 days later normal	6	Neg.	Neg.
W.L. 2 yr. W.M.	3	Critically ill. Very cyanotic and dyspneic. T. 103.6	2.0 gm. stat. 0.5 gm. q. 6 h.	22	Admission: Diffuse patchy pneumonia. 5 days later normal	6	Not done	Not done
M.McC. 2 yr. W.F.	1	Critically ill. Very dyspneic. Otitis medin. T. 104	1.5 gm. stat. 0.4 gm. q. 6 h.	28	Admission: Bilateral patchy pneumonia. 7 days later normal	16	Not done	Not done

II—CONT'D

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	--	Many	7.3	None	Prompt and striking recovery in less than 24 hours after sulfapyridine.
Sterile	--	Neg.	10.0	None	Improvement after sulfapyridine not striking because child was not very ill before treatment.
Sterile	23	Neg.	8.6	None	Rapid improvement after sulfapyridine and oxygen. Temperature normal within 24 hours but dyspnea remained for 24 hours longer.
Sterile	Neg.	Neg.	4.5	None	Temperature normal and child greatly improved 24 hours after sulfapyridine.
Sterile	6	Few	8.3	None	Rapid fall in temperature. Uneventful convalescence following sulfapyridine.
Sterile	--	Many	4.5	None	Remarkable improvement following sulfapyridine and oxygen. Within 24 hours temperature normal. Child no longer critically ill. Moderate dyspnea continued 24 hours longer. Probably mixed pneumococcus and streptococcus pneumonia.
Sterile	15	Few	3.4	None	Temperature normal 24 hours after sulfapyridine begun and respirations decreased from 60 on admission to 20 next day. Uneventful convalescence.

TABLE

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
J.M. 2 yr. W.F.	3	Severely ill. Dyspnea. Cyanosis. Otitis media. T. 104	2.0 gm. stat. 0.5 gm. q. 6 h.	16	Admission: Homogenous density, right upper lobe. 7 days later normal	14	Not done	Not done
J.R. 2 yr. W.M.	1	Severely ill. Cyanosis. Dyspnea. T. 102.6	2.0 gm. stat. 0.5 gm. q. 6 h.	28	Admission: Homogenous density, right upper lobe. 8 days later normal	15	Neg.	Not done
D.S. 2 yr. W.F.	1	Moderately ill. Dyspnea. Meningismus. Otitis media. T. 105.4	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Homogenous density, left lower lobe. 5 days later normal	14	Neg.	Neg.
D.B. 2½ yr. W.F.	2	Moderately ill. Dyspnea. T. 103.2	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Homogenous density, right lower lobe. 4 days later normal	14	Not done	Not done
W.B. 2½ yr. W.M.	3	Moderately ill. Dyspnea. T. 104.2	1.5 gm. stat. 0.5 gm. q. 6 h.	22	Admission: Homogenous density, right lower lobe. 10 days later normal	2	Neg.	Neg. for 2. Pos. for 19
A.B. 2½ yr. W.M.	3	Moderately ill. Moderate dyspnea. T. 104.6	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Diffuse patchy pneumonia. 3 days later clearing	18	22	Not done

II—CONT'D

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	14	Few	7.8	None	Temperature normal. Dyspnea and cyanosis gone within 24 hours after sulfapyridine.
Sterile	--	Many	3.7	None	Temperature normal within 24 hours after sulfapyridine but dyspnea still present 24 hours longer, and child still appeared ill during this time. Thereafter, seemed well and convalescence uneventful.
Sterile	Neg.	Very many	10.2	None	Temperature normal and child appeared well within 24 hours after sulfapyridine. Convalescence uneventful.
Sterile	--	Many	8.7	None	Temperature normal and child more alert within 24 hours. Convalescence uneventful.
Sterile	19	Neg.	7.2	None	Type 2 pneumococcus in nasopharynx. Temperature normal within 24 hours after sulfapyridine. Sulfapyridine discontinued in 11 days. 48 hours later temperature rose to 104.8. Right myringotomy done and sulfapyridine begun. Temperature returned to normal in 16 hours. Type 19 pneumococcus cultured from nasopharynx and ear—same type as patient (J.H.) in next bed. Uneventful convalescence.
Sterile	--	Neg.	6.3	Granulocytopenia	Temperature normal, dyspnea less and general improvement within 24 hours after sulfapyridine. Temporary granulocytopenia 6 days after admission.

TABLE

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR		
						NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
J.B. 3 yr. W.M.	2	Moderately ill. Respirations accelerated. Otitis media. T. 105	2.4 gm. stat. 0.6 gm. q. 6 h.	32	Admission: Homogenous density.	2	Not done	Not done
S.S. 3 yr. W.F.	1	Moderately ill. Slight dyspnea. T. 103.6	3.0 gm. stat. 0.75 gm. q. 6 h.	24	Admission: Homogenous density, left lower lobe. 12 days later normal	19	Neg.	Neg.
J.T. 4 yr. W.F.	3	Moderately ill. Only slight dyspnea. T. 104.2	2.5 gm. stat. 0.25 gm. q. 6 h.	20	Admission: Homogenous density, right upper lobe. 3 days later normal	Neg.	14	Neg.
G.K. 4 yr. W.M.	2	Severely ill. Moderate dyspnea. Bilateral otitis media. T. 104	2.0 gm. stat. 0.5 gm. q. 6 h.	24	Admission: Patchy pneumonia, bilateral. 10 days later normal	18	18	Neg.
D.DeH. 4 yr. W.M.	1	Critically ill. Delirious. Otitis media. T. 104.6	2.0 gm. stat. 0.5 gm. q. 6 h.	36	Admission: Homogenous density, left lower lobe. 7 days later normal	6	Not done	Not done
R.P. 5 yr. W.M.	1	Critically ill. Extreme dyspnea and cyanosis. Placed in oxygen. T. 105	4.0 gm. stat. 0.75 gm. q. 6 h.	28	Admission: Very extensive diffuse patchy pneumonia. 19 days later normal	29	Neg.	Neg. for 29. Pos. for 8

II—CONT'D

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	2	Neg.	6.6	None	Temperature normal and patient improved about 24 hours after admission. Drainage from middle ear 4 days. Uneventful convalescence.
Not done	--	Neg.	6.6	None	Temperature normal within 24 hours after sulfapyridine. Uneventful convalescence.
Sterile	--	Few	Not done	Granulocytopenia	Appeared more alert and seemed entirely well 24 hours after sulfapyridine. Granulocytopenia on 7th day of sulfapyridine but disappeared when drug discontinued.
Sterile	Neg.	Few	7.8	None	Temperature normal and greatly improved 24 hours after sulfapyridine. Middle ear drained 6 days. Uneventful convalescence.
6	Neg.	Not done	5.1	None	Striking improvement after sulfapyridine. Within 36 hours child appeared completely well.
Sterile	--	Neg.	10.2	None	Temperature fell from 105 to normal in 24 hours after sulfapyridine. At that time appeared out of danger but dyspnea present 48 hours longer. Pneumonia due to Type 29 pneumococcus. Three days after sulfapyridine discontinued developed upper respiratory infection and Type 8 pneumococcus found in nasopharynx. Child in next bed (G.L.) had pneumonia due to Type 8 pneumococcus. Uneventful convalescence from respiratory infection.

TABLE

NAME, AGE, COLOR, SEX	DURATION OF PNEUMONIA BEFORE SULFAPYRIDINE BEGUN, DAYS	CLINICAL CONDITION BEFORE SULFAPYRIDINE	DOSE OF SULFAPYRIDINE	DURATION OF FEVER AFTER SULFAPYRIDINE BEGUN (NORMAL 99.2° R.) HOURS	X-RAY FINDINGS	CULTURES FOR NASOPHARYNX		
						BEFORE SULFAP.	DURING SULFAP.	AFTER SULFAP.
G.L. 5 yr. W.M.	1	Moderately ill. Otitis media. T. 104.2	3.0 gm. stat. 0.75 gm. q. 6 h.	32	Admission: Homogenous density, right upper lobe. 10 days later normal	8	8	8
N.L. 7 yr. W.F.	1	Moderately ill. Otitis media. T. 104.2	4.0 gm. stat. 1.0 gm. q. 6 h.	12	Admission: Homogenous density, left lower lobe. 6 days later normal	4	Not done	4 and 3
J.H. 8 yr. W.M.	Not known	Critically ill. Marked dyspnea and cyanosis. Placed in oxygen. Otitis media. T. 102.4	4.0 gm. stat. 1.0 gm. q. 6 h.	20	Admission: Bilateral patchy pneumonia. 10 days later normal	19	Neg.	19
B.L. 8 yr. W.F.	3	Moderately ill. T. 102.6	2.0 gm. stat. 0.75 gm. q. 6 h.	32	Admission: Bilateral patchy pneumonia. 5 days later normal	19	Not done	Neg.
M.O. 8 yr. W.F.	1	Moderately ill. Slight dyspnea. T. 103	3.0 gm. stat. 0.5 gm. q. 6 h.	16	Admission: Homogenous density, left lower lobe. 10 days later normal	4	Not done	Not done

II—CONT'D

PNEUMOCOCCI TYPE		THROAT CULTURE FOR BETA STREPT.	CONCEN. SULFAP. IN BLOOD (3RD DAY MG. %)	ILL EFFECTS OF SULFAP.	SUMMARY OF CLINICAL COURSE
BLOOD	EAR				
Sterile	--	Neg.	6.4	None	Prompt fall in temperature after sulfapyridine. Otitis media subsided without drainage. Uneventful convalescence.
Sterile	4	Few	11.8	Hematuria	Rapid fall in temperature following sulfapyridine. Drug stopped after 2 days because of gross hematuria which cleared rapidly. 2 days after drug discontinued, microscopic examination of urine negative but Addis counts showed increased red cells until 10 days later. PSP showed decreased kidney function until 12 days after onset of hematuria. Had acute nephritis after scarlet fever 1 year ago.
Sterile	19	Many	8.4	None	Probably mixed pneumococcus and streptococcus pneumonia. Temperature became normal abruptly but no dramatic change in dyspnea, cyanosis, or general condition. Gradual definite improvement during first 48 hours. Middle ear drained 10 days. Uneventful convalescence.
Sterile	--	Neg.	12.2	Frequent vomiting	Child scarcely ill on admission. Uneventful convalescence.
4	--	Neg.	Not done	None	Extremely rapid fall in temperature from 105 to normal in 12 hours. Child not very ill on admission. Uneventful convalescence.

on admission. Most of the patients at the Sydenham Hospital, like those at the Harriet Lane Home, were not critically ill on admission. There were 8 patients, however, who were desperately ill when they entered the hospital.

The possible ill effects of the drug must always be kept in mind; hematuria, granulocytopenia, and anemia are the most usual toxic manifestations. We believe that leucocyte counts, hemoglobin determinations, and urine examinations should be carried out at least every other day on all patients receiving the drug in order to detect the development of these untoward effects as early as possible. Thus far, in our experience, the ill effects of the drug have been only temporary and not sufficiently serious to make its general use in pneumonia seem unwise. However, this belief may prove to be erroneous when greater experience with the drug is gained. Data on this point must be carefully gathered before a true evaluation of the usefulness of sulfapyridine in pneumonia can be made.

SUMMARY

Seventy-one patients proved to have pneumonia by x-rays were treated with sulfapyridine. Typable pneumococci were isolated from the nasopharynx in each instance.

Thirty-three of these patients had primary pneumonia. In 38 of them the pneumonia was associated with measles.

All the patients recovered. In nearly every case the temperature became normal and definite improvement took place within forty-eight hours after institution of treatment.

The method of administration of the drug is described and certain untoward effects are mentioned.

The presence of pneumococci in the nasopharynx of a number of patients after the withdrawal of sulfapyridine was noted.

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BLOOD STUDIES OF VITAMIN C DURING PREGNANCY, BIRTH, AND EARLY INFANCY

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PART I (S. H. JACKSON, PH.D.)

CONSIDERABLE investigation has been made lately of the errors inherent in the determination of ascorbic acid in blood and urine, and as a result of these investigations it has been shown that a large proportion of previously published results are valueless, either because of failure to report the method of analysis and the precautions taken to limit the chance of error, or through lack of proper control of the conditions of analysis. In the first section of this paper we accordingly report the method of analysis used to determine the ascorbic acid content of the blood specimens and the steps we took to insure the reliability of our results.

Rosen and Evelyn[1] have outlined the principles of a method for the determination of ascorbic acid using the Evelyn photoelectric colorimeter.[2] Mindlin and Butler[3] have recently published a method for the determination of ascorbic acid in plasma on these principles. They employed the Evelyn photoelectric colorimeter. The method was first described to us in a personal communication from Evelyn. We made two minor changes in the strength and amount of reagents used, but it was essentially the same as that described by Mindlin and Butler. A few additional precautions in collection and preparation of the blood specimens were taken, with greatly increased reliability of the results produced.

Blood specimens of approximately 5 ml. were collected in the presence of 1 mg. of potassium cyanide and 2 mg. of potassium oxalate, shaken, and immediately placed in ice water. They were kept at 0° C. until they could be analyzed, in no case more than one hour after collection. In this way the loss by oxidation of the ascorbic acid was reduced to a maximum of less than 10 per cent. Without the precaution of cooling the specimen, as much as 50 per cent of the ascorbic acid could be lost in the first hour after collection of the sample. Arthur Abt[4] has questioned the advisability of adding cyanide to the blood specimen. He claims that it does not prevent oxidation of the ascorbic acid and that it introduces a reducing substance that increases the apparent ascorbic acid content of the blood. We have no personal data on the effect of cyanide on the rate of oxidation of

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ascorbic acid in blood. However, we tested the sample of cyanide used during the course of this research and found no reducing substance such as Abt detected.

The next step after collection of the blood was the preparation of a suitable filtrate for the analysis. The specimen was centrifuged and the clear plasma drawn off. Two ml. of plasma were mixed with 3 ml. of water and 5 ml. of a 5 per cent metaphosphoric acid solution to precipitate the proteins. The solution was then filtered. It was found that the use of whole blood instead of plasma resulted in the complete destruction of the ascorbic acid. This was due to the oxidative action of hemoglobin during the precipitation of the blood proteins. If the specimen was partially hemolyzed so that the plasma contained some hemoglobin, this action was found still to take place so that some loss of ascorbic acid resulted, depending on the extent of hemolysis. For this reason, any specimens showing more than the slightest trace of hemolysis were discarded.

The actual determination of the ascorbic acid content of the metaphosphoric acid—plasma filtrate, essentially that described by Mindlin and Butler, was performed as follows:

To 5 ml. of plasma filtrate in a colorimeter tube was added 5 ml. of the indophenol dye solution from a rapid delivery pipette calibrated to deliver 5 ml. in 5 seconds. The solution was then rapidly mixed and placed in the colorimeter and the first reading taken ten seconds after beginning addition of the dye. The blank dye sample was made up and read in the same manner, 2 per cent metaphosphoric acid being used in place of the filtrate. The dye solution was diluted from a stock solution for daily consumption and was made up in such concentration that the blank gave a galvanometer reading of about 45. About 100 mg. of sodium acetate per 100 ml. of dilute dye solution was added to keep it alkaline. We found that more than this was not necessary. The reduction of the dye by the metaphosphoric acid was very slight and compensation for such as occurred was made by the blank.

Results were calculated from the equation $M = \frac{L_1 - L_2}{K}$ where M = mg. ascorbic acid in volume of filtrate added to the tube (i.e., in 5 ml. filtrate equivalent to 1 ml. plasma).

L_1 and L_2 are expressions of the optical density of the dye blank and the sample respectively and are calculated from the galvanometer reading G by the equation $L_x = 2 - \log G$.

K is a constant and was found to have a value of 8.4 within narrow limits. Three different brands of ascorbic acid and two brands of dye all gave this average value.

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PART II (CHARLES E. SNELLING, M.B.)

There has been much interest in vitamin C nutrition with the advent of more accurate methods of estimation. Using the method outlined previously[1] we have determined the plasma ascorbic acid in pregnancy and early infancy.

The plasma ascorbic acid of a group of women during pregnancy and immediately post partum was measured (Table I).* The average for the group from two to five months' gestation was 0.6 mg. per cent. At six months' gestation it was 0.51; at seven months' gestation it was 0.49; at eight months' gestation it was 0.43, and at term, 0.42 mg. per cent. Most of the latter were women who had commenced to have labor pains. Immediately after delivery the average of plasma ascorbic acid was 0.23 mg. per cent. Our figures suggest that there is possibly a slight fall in the level of plasma ascorbic acid with increasing months of pregnancy. Ingalls and co-workers have previously reported this.[2] There is a marked fall between the average at term and immediately after delivery. The difference is probably the result of some factor incident to labor. Fleming and Sandford reported that the levels immediately post partum were lower than those obtained one week later.[3]

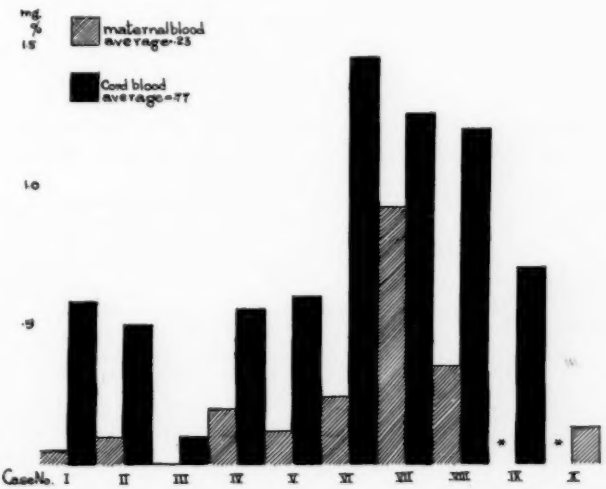

Chart 1.—Simultaneous estimation of the plasma ascorbic acid of cord and maternal blood. *indicates blood hemolyzed—unsuitable for estimation.

The ascorbic acid of cord and maternal blood plasma was estimated immediately following delivery (Chart 1). The cord blood ascorbic acid varied from 0.1 mg. to 1.47 mg. per cent with an average of 0.77

*We wish to express our appreciation to Professor W. A. Scott of the Department of Obstetrics, and his staff, for their cooperation and efforts in obtaining many of the samples.

mg. per cent. The maternal blood varied from 0 to 0.92 mg. per cent with an average of 0.23 mg. per cent. In every instance the maternal blood content of ascorbic acid was considerably less than the fetal blood. The average cord blood estimations are higher also than the average for maternal blood at term before labor started (Table I). Ingalls has reported similar results. One concludes that the fetus acts as a parasite to the mother in regard to vitamin C.

TABLE I

PLASMA ASCORBIC ACID OF PREGNANT WOMEN

TERM	CASES NO.	AVERAGE MG. %
Up to 5 mo.	12	0.6
6 mo.	6	0.51
7 mo.	11	0.49
8 mo.	10	0.43
Full term	8	0.42
After delivery	13	0.23

The plasma ascorbic acid was estimated in a number of breast-fed babies from 2 weeks to 5 months of age, and at the same time the mother's breast milk was tested for the content of ascorbic acid (Table II). In thirteen totally breast-fed babies not receiving additional vitamin C, five had ascorbic acid measurements of more than 1 mg. per cent; five had 0.75 to 1.0 mg. per cent. Of the thirteen breast milks obtained at the same time, nine had measurements of 4 mg. per cent of ascorbic acid or over, and four were below 2.5 mg. per cent.

TABLE II

RELATION OF PLASMA ASCORBIC ACID OF BREAST-FED INFANTS TO MOTHER'S BREAST MILK

INFANTS MG. %	CASES NO.	BREAST MILK MG. %
1.0 to 2.0	5	All above 4
0.7 to 1.0	5	*4 cases above 4
0.0 to 0.5	3	All below 2.5

*1 case below 2.5.

The five babies with plasma ascorbic acid content above 1 mg. per cent were fed on breast milk with more than 4 mg. per cent ascorbic acid. One of the five babies with ascorbic acid content between 0.75 and 1.0 mg. per cent was receiving breast milk with 1.9 mg. per cent, and all three babies with ascorbic acid content below 0.5 mg. per cent were receiving breast milk with less than 2.5 mg. per cent of ascorbic acid. Ingalls reported that nursing babies at 2 weeks of age receiving breast milk containing 4.6 mg. per cent had an average plasma ascorbic acid of 0.87 mg. per cent. If the diet of the mother was supplemented with additional vitamin C, they found that the content in the breast milk was raised and also the level in the blood plasma of the infant was higher. It appears then that, if the ascorbic acid level of the breast milk is

over 4 mg. per cent and if the baby is totally breast fed, the ascorbic acid level of the plasma is above 0.7 mg. per cent which Ingalls states is the normal level.

The plasma ascorbic acid was measured on artificially fed babies of ages ranging from 1 week to 3 months, who were receiving no additional vitamin C (Table III). The plasma ascorbic acid varied from 0.05 mg. per cent up to 0.52. The average figure was 0.19 mg. per cent. It appears that the artificially fed infant should receive additional vitamin C from at least the time he is 2 weeks of age. Ingalls found the average plasma level of ascorbic acid in artificially fed infants at 2 weeks of age to be 0.3 mg. per cent.

TABLE III

PLASMA ASCORBIC ACID

	12 ARTIFICIALLY FED INFANTS* MG. %	15 BREAST-FED INFANTS* MG. %
Highest	0.52	1.6
Lowest	0.05	0.0
Average	0.19	0.91

*All infants under 3 months of age.

SUMMARY

We have measured the ascorbic acid of the plasma of pregnant women. There seems to be a slight fall toward the end of pregnancy. Factors incident to labor lower the ascorbic acid in the maternal blood. The fetus acts as a parasite and has higher levels than maternal blood taken ante partum. Totally breast-fed babies are well supplied with vitamin C if the ascorbic acid of the milk is greater than 4 mg. per cent; if the ascorbic acid is below 2 mg. per cent in the breast milk, there is likelihood of a deficiency in the baby. In artificially fed babies not receiving additional vitamin C, the level of ascorbic acid in the blood is low.

As a result of these studies, the following recommendations are made: Artificially fed babies should receive additional vitamin C from the time they are 2 weeks of age. The mothers of breast-fed babies should have adequate vitamin C in the diet, and, if there is any question of lack in the mother's diet, the baby should receive additional vitamin C.

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TREATMENT OF CRYPTORCHIDISM WITH GONADOTROPIC SUBSTANCE

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IN 1926 Aschheim and Zondek[1] reported having been able to induce sexual maturity in immature rats by means of pituitary transplants. Continuing their research, they further demonstrated[2] (1928) that a substance present in the urine of pregnant women could stimulate the sex glands. Likewise, Engle[3] (1929) showed that injections of pregnancy urine into immature rats caused an increased rate of growth of the sex organs. Taking advantage of these findings, Schapiro[4] (1930) obtained satisfactory results in treating thirteen children with genital underdevelopment and cryptorchidism. He used the water-soluble extract of pregnancy urine, with the result of complete descent in ten cases, partial descent in three cases, and no failures. The endocrine treatment of cryptorchidism was further stimulated by the work of Engle[6] (1932), when he demonstrated that by injecting pregnancy urine or the active principle of the anterior pituitary gland he could bring about descent of the testes in monkeys with delayed puberty. Since then, in the past six years, there have appeared frequent reports on the treatment of cryptorchidism with gonadotropic substance, and mostly with very gratifying results (Table I). The work that I am herewith reporting on the treatment of cryptorchidism with gonadotropic substance presents less favorable results, but nevertheless worthy of notice, especially as I feel that my findings, based on rigid criteria, represent a true figure of the best possible results obtainable in a carefully selected group of true cases of cryptorchidism.

CHOICE OF CASES

All the cases in this series were from the Out-Patient Department of Mount Sinai Hospital, New York. Only children over four years of age were included in our group for treatment. Most of them were seen at intervals for a period of three to six months before treatment was instituted. In addition, each boy selected for treatment satisfied the following criteria:

1. Each boy was examined both in standing and reclining positions by at least three physicians who had to be unanimous in the diagnosis.
2. At no time in the past history of the child had the testicle been seen or felt in the scrotum.
3. Testicles could not be pulled or forced into the scrotum.
4. Testicle could not be brought down into the scrotum after twenty to thirty minutes under a heat lamp or in a warm bath.

From the Pediatric Service of Dr. Béla Schick, Mount Sinai Hospital.

5. Descent after one, two, or even three injections ruled a case out. We felt that this type would have descended spontaneously.

TABLE I

REVIEW OF LITERATURE

AUTHOR	NUMBER OF PATIENTS	AVERAGE AGE	TOTAL NUMBER OF UNDESCENDED TESTES	NUMBER OF TESTES DESCENDED	% OF TESTES DESCENDED	NUMBER OF CASES WITH DESCENT	% OF CASES WITH DESCENT
Goldman and Stern[8] 1933	2	13½	2	2	100	2 of 2	100
Schapiro[4] 1930	13	9-27				13	100
Aberle and Jenkins[10] 1934	4	7	5	2	40	2 of 4	50
Cohn[11] 1934	5	9½	6	5	84	5 of 6	84
Kunstadter and Robbins[12] 1934	3	10	5	5	100	3 of 3	100
Rubinstein[13] 1934	1	10½	2	1 partial	87	1 of 1	87
Sexton[14] 1934	6	12½	9	7	78	4 of 6	66
Brosius[15] 1935	9	3-38	12	9	75	6 of 9	66
Dorff[16] 1935	8	8½	10	9	90	7 of 8	87
Huberman and Israeloff[17] 1935	6	11	8	5	63	3 of 6	50
Kunstadter[22] 1936	13		23	19	82	10 of 13	78
Priestly and Cohen[18] 1935	2	12	4	1	25	½ of 2	25
Sippe[19] 1935	1	10	2	2	100	1 of 1	100
Spence and Scowen[20] 1935	33	4-26	45	29	64	21 of 33	63
Webster[21] 1935	11	11	15	13	86	10 of 11	91
Rubinstein[23] 1936	8	10½	12	5	42	3½ of 8	44
Goldman, Stern, and Lapin[24] 1936	11	13½	19	15	89	9 of 11	81
Hess, Kunstadter, and Saphir[34] 1937	13	5-14	26	19	74	9 of 13	72
Thompson and co-workers[35, 36, 37], 1937-1938	28	1½ to 17	36	8	23	8 of 28	28

TABLE I—CONT'D

AUTHOR	NUMBER OF PATIENTS	AVERAGE AGE	TOTAL NUMBER OF UNDESCENDED TESTES	NUMBER OF TESTES DESCENDED	% OF TESTES DESCENDED	NUMBER OF CASES WITH DESCENT	% OF CASES WITH DESCENT
Cramer[29] 1937	20	5-13	30	19	63	13 of 20	66
Werner and coworkers[28] 1936	17	5-13	33	24	73	12 of 17	72
Bigler and coworkers[38, 39] 1938	A.P.L. 23 Pit. 32 Both 16	2-13	31 40 20	14 7 5	45 18 25	8½ of 23 5 of 32 4 of 16	50 16 25
Sexton[26] 1936	15	5-18	23	17	72	10 of 15	61
Gordon[25] 1936	28	2-14	44	33	75	21 of 28	75
Molitch[40] 1937	11	11-16	15	11	74	7 of 11	63
Farmer[30] 1937	32	1-14	40	22	45	16 of 32	50
Rony[31] 1937	6	11-33	10	6	60	3½ of 6	60
Von Gelderen[27] 1936	64	8-14	97	57	60	39 of 64	61
Mimpriss[32] 1937	20	4-14	30	11	34	6 of 20	30
Hess and Kunstadter[33] 1937	39	2-15	68	56	82	28 of 39	72
TOTAL	468		682	431	63	286	61
Zelson 1938	26	4½-12½	34	11	32	8 of 26	31

With these criteria, twenty-six cases were selected for treatment. Eighteen were unilateral and eight were bilateral cases of cryptorchidism, thus totaling thirty-four undescended testicles.

TREATMENT

The gonadotropic principle used in the treatment of each child was obtained from the urine of pregnant women. This substance (follutein) had a potency of 1,000 units per 1 c.c. Each boy was given three to six injections a week for a period ranging from two weeks to fourteen months. The boys treated early in the series received 100 to 200 units at an injection; those treated later in the series received 200 to 500 units at an injection; several received 1,000 units at an injection. The total dosage varied between 1,350 and 39,100 units. All the injections were given intramuscularly. Before considering a case unsuccessful, a minimum total dosage of 5,000 to 10,000 units was given. None of the children showed any general reactions even when the larger doses were given, though the site of injection was, as a rule, painful for several hours. There were, however, reports that several of the children had become

problem children, a condition that improved after the cessation of the treatment. A number of boys received two and three courses of treatment at six-month intervals, each succeeding course with a higher dosage per injection.

RESULTS

Twenty-six boys with 34 undescended testicles were treated with gonadotropic hormone (Table II). In 18 cases the condition was unilateral; in 8 cases it was bilateral. Complete descent occurred in 8 cases, i.e., in 31 per cent of the patients. Of these, 5 were unilateral cases of cryptorchidism, and 3 were bilateral. The condition was considered as having successfully responded to treatment only when the testicles descended into the scrotum. We did not include among our successful cases those in which the testicles came down from the upper part of the canal to the lower part, or those in which an abdominal testicle became palpable in canal. In the 8 successful cases 5 of the patients responded to less than 5,000 units; 6 of them responded to treatment within three months. The penis, testicles, and scrotum became larger during the course of treatment in every case. A few developed pubic hair. However, it was noted that on re-examination of the patients in the unsuccessful cases from three to six months following the cessation of treatment the testicles which had enlarged during treatment had shrunk back to their original pre-treatment size. The penis continued to remain large. During the course of the treatment, 7 of the 26 boys were reported as being "bad boys" in school. When the injections were discontinued, however, this condition improved.

DISCUSSION

Although numerous reports have been published on the treatment of cryptorchidism with gonadotropic substance, no definite conclusions have as yet been formulated. The type of case, the optimum age for treatment, the dosage, and the length of treatment have certainly not been determined as yet. In summarizing the literature, it is quite apparent that no two physicians feel alike. It is my impression, however, that the opinion is gradually crystallizing to the effect that the most promising cases for treatment are those of boys who have no apparent obstruction in the canal, who manifest some apparent endocrine disturbance, and who are close to puberty. It is also believed that most of the children who respond to treatment do so within a period of three months, and certainly before 10,000 units of gonadotropic hormone has been given. I believe that the massive doses which have recently been recommended need not be given and that the injections need be given no more frequently than three times per week. I have in mind possible harm that may result from too large dosages and too frequent injections. Stimulation and growth of the genitals occur in almost every boy, not only in our series but also in many of those reported in the literature. The risks involved

TABLE II

SUMMARY OF CASES TREATED

NAME	AGE (YR.)	GENERAL APPEARANCE	GENITALS	NUMBER OF UNDESCENDED TESTICLES AND LOCATION	DOSAGE	SUBSTANCE GIVEN	TOTAL DOSAGE (UNITS)	LENGTH OF TREATMENT	RESULT	EFFECT ON GENITALS AND GENERAL CONDITION
G. F.	4½	Normal	Penis normal. Scrotum small. Rt. testis in canal.	1 Canal	50-100 U. 3 × wk. 200 U. 3 × wk.	Follutein Antophysin	1,700 4,850	3 mo. 1 year later 2 mo.	Down in scrotum	Penis and scrotum larger. One year after original treatment testis in canal. Down again on second course of treatment.
N. P.	4½	Normal	Left hydrocele, Rt. testis in canal.	1 Canal	500 U. 3 × wk.	Follutein	3,200	2½ wk.	Down in scrotum	Penis larger. Negative.
M. T.	6	Normal	Normal. Rt. testis in canal.	1 Canal	200-500 U. 3 × wk.	Follutein	9,850	3 mo.	Negative	Penis and scrotum larger. Became unruly in school.
J. D.	6	Normal	Normal. Rt. testis in canal.	1 Canal	200 U. 3 × wk.	Follutein	10,000	3 mo.	Negative	Penis larger.
G. D.	6½	Small for age	Small penis. Small scrotum. Both testes in canal.	2 Canal	150 U. 3 × wk. 200 U. 3 × wk.	Antuitrin S Follutein	3,850 9,550	10 wk. 6 mo. later 20 wk.	Negative Negative	Penis larger. Testes at external ring. Two courses 6 months apart.
J. G.	7	Small for age	Penis small. Scrotum small. Neither testis palpable.	2 Abdominal	100-200 U. 3 × wk.	Follutein	7,750	3 mo.	Negative	Penis larger. Testes palpable in canal. Became unruly in school.
E. O.	7½	Normal	Both testes in canal.	2 Canal	100 U. 3 × wk.	Follutein	1,320	4 wk.	Down in scrotum	
B. L.	8	Normal	Normal. Rt. testis not palpable.	1 Abdominal	200 U. 5 × wk.	Follutein	4,950	5 wk.	Negative	Penis larger. Became unruly in school.

TABLE II—CONT'D

M. L.	8	Normal	Normal. Rt. testis in canal.	1 Canal	200 U. 3 × wk.	Follutein	5,700	6 wk.	Negative	Negative. Hernia on rt. side.
J. F.	8	Normal	Normal. Rt. testis not felt.	1 Abdominal	200 U. = 500 3 × wk.	A. P. L.	7,800	12 wk.	Testicle in upper part of scrotum	Became unruly in school. Penis larger.
P. L.	8	Normal	Normal. Rt. testis in canal.	1 Canal	500 U. 3 × wk.	Follutein	5,100 10,000	2 mo. 6 mo. later 3 mo.	Negative Negative	Penis larger.
V. C.	9	Small for age	Scrotum small. Rt. testis in canal.	1 Canal	200 U. 3 × wk.	Antophysin	5,000	9 wk.	Down in scrotum	Developed a hernia, which was repaired. Penis and scrotum larger.
T. L.	9	Normal	Normal. Rt. testis in canal.	1 Canal	100-200 U. 3 × wk.	Follutein	1,450	4 wk.	Down in scrotum	Penis larger.
M. G.	10	Normal	Scrotum small. Left testis not felt.	1 Abdominal or atrophied	200 U. 3 × wk.	Follutein	8,600	15 wk.	Negative	Has scar of operation four years previous in attempt to reduce testis. No results.
M. M.	10	Small for age	Scrotum small. Left testis in canal.	1 Canal	100 U. 5 × wk for 6 wk. 200 U. 3 × wk. for 5 wk.	Follutein	6,500	3 mo.	Negative	Testicle was larger. Penis larger. Became unruly in school.
D. H.	10	Normal	Scrotum small. Neither testicle palpable.	2 Abdominal	200 U. 3 × wk. 200 U. 6 × wk. 500 U. 3 × wk.	Follutein Follutein Follutein	6,900 2,500 10,000	2 mo. 2 wk. 7 wk.	Negative Negative Negative	Second course given 6 mo. after first, and third course two years after second. Testes in canal. Became unruly in school.
R. W.	10	Froelich type mentally slow	Rt. testis not palpable. Penis and scrotum small.	1 Abdominal	200 U. 3 × wk. 500 U. 3 × wk.	Follutein	14,950	9 wk. 7 wk.	Negative Negative	Testicles, penis, and scrotum larger. Rt. testicle could be pushed to external ring.

TABLE II—CONT'D

NAME	AGE (YR.)	GENERAL APPEARANCE	GENITALS	NUMBER OF UNDESCENDED TESTICLES AND LOCATION	DOSAGE	SUBSTANCE GIVEN	TOTAL DOSAGE (UNITS)	LENGTH OF TREATMENT	RESULT	EFFECT ON GENITALS AND GENERAL CONDITION
D. S.	10½	Obese Froelich type	Neither testis palpable. Scrotum, penis small.	2 Abdominal	200 U. 3 × wk. 500 U. 3 × wk.	Follutein	39,100	14 mo.	Negative	Both testes palpable in canal. With thyroid, lost 30 pounds. Penis and scrotum larger. Pubic hair.
K. S.	10½	Small for age	Normal. Rt. testis small in canal.	1 Canal	200 U. 3 × wk. 500-1000 U. 3 × wk.	Follutein	10,000	5 mo.	Negative	Penis and scrotum larger.
G. S.	10½	Normal	Normal. Left testis in canal. Rt. not felt.	2 1 Canal 1 Abdominal	200 U. 3 × wk. 250 U. 3 × wk.	Follutein Follutein	10,000 1,500	16 wk. 2 wk.	Both in scrotum	Return to canal after 3 mo. Second course brought testes down again. Penis and scrotum larger.
L. T.	11	Small for age	Scrotum small. Left testis in canal.	1 Canal	500-1000 U. 3 × wk.	Follutein	10,000	5 wk.	Negative	Testicle in canal larger. Penis and scrotum larger.
A. S.	12	Normal	Rt. testicle not palpable. Left in lower end of canal.	2 1 Canal 1 Abdominal	200 U. 3 × wk.	Follutein	8,900	4 mo.	Both in scrotum	Developed hernia on left side. Penis larger.
J. D.	12½	Normal	Rt. testicle in canal.	1 Canal	100-200 U. 3 × wk.	Follutein	4,625	2 mo.	Negative	Toreck operation for repair. No obstruction found at time of operation.
R. B.	11½	Normal	Both in canal.	2 Canal	200 U. 4 to 5 × wk.	Follutein	8,850	10 wk.	Negative	Penis larger. Rt. testis at external ring. Pubic hair. Operation for repair. No obstruction found.
I. S.	11½	Normal	Left testis in canal.	1 Canal	200 U. 6 × wk. 500-1000 U. 3 × wk.	Follutein	6,100 10,000	5 wk. 5 wk.	Negative Negative	Hernia on left side repaired and testis brought down. Testicle found bound down in canal.
G. L.	11	Normal	Rt. testis in canal.	1 Canal	500-1000 U. 3 × wk.	Follutein	10,600	5 wk.	Negative	Penis larger.

in such premature stimulation and activation have certainly not been determined. It is interesting to note that during the period of treatment seven of my patients manifested a change in conduct to such a degree that they were reported as having become problem children, a condition which fortunately improved when treatment ceased. What other changes occurred or what effect the injections may have on the future growth and development, not only of the genital system but also on the body as a whole, cannot be estimated at present; only the future may reveal the facts. Moreover, the possibility of spontaneous late descent without excessive artificial stimulation should not be ruled out of consideration. It has been shown[7] that "a normal prepubertal undescended testicle does not differ histologically and functionally from a prepubertal scrotal testicle and that the function of the testicle is only important with the onset of puberty." It is well known that spontaneous descent occurs at various times from birth through puberty. Bigler and his co-workers[38] report, "In a series of 450 newborn boys, 10 per cent had undescended testicles, whereas in a similar series of premature boys, there was an incidence of 32 per cent." Drake[9] claims that in 65 per cent of all cases of maldescent descent will take place at or near puberty. In two series of boys between 9 and 20 years of age, totaling 528 cases, he found twenty-seven cases, or 5 per cent of maldescent. Of 18,140 boys admitted to Hospital for Ruptured and Crippled, New York City, 3 per cent were reported as having undescended testicles. On the other hand, Goetsch[5] found only two to five cases of undescended testicles per 1,000 (0.2 to 0.5 per cent) among army recruits. The Medical Corps of the United States Army has reported that 3.1 (0.3 per cent) of each 1,000 recruits had undescended testicles.

An analysis of the above figures tends to show that there certainly must be a spontaneous descent in a great number of the cases seen before puberty. Because of these facts, one would be inclined to feel that treatment should not be begun before nine or ten years of age. However, it is interesting to note that in a number of the papers reviewed the following data were obtained: Cohn[11] had 4 successful cases, of whom 3 were 10 years old or younger. Dorff[16] reported 7 successful cases, with 5 under 10 years of age. Spence and Scowen,[20] in their series of 33 cases, had 8 boys under 10 years of age; 7 of these responded to treatment. Thompson and co-workers[37] reported 7 successful cases, with all except one under 10 years of age. Cramer[29] reported 14 successes, with 7 under the age of 10 years. Hess and Kunstadter[33] had 28 successful results in a series of 39 children. Twenty-two children in this series were under 10 years of age. Of these, 17 boys responded successfully to treatment. In my group of 26 children, 8 responded to treatment with complete descent of the testicles. Of the 8, 6 were boys under ten years of age.

On the basis of the above facts it would seem that treatment is more successful in the children under 10 years of age. Of course, it may be

argued that in a majority of these the testes would have descended spontaneously had they been left alone. In my group of children, however, because of the strict criteria for choice, I feel that there would not have been a spontaneous descent in any of the cases. The question of treating the children early in life should, I believe, be given further consideration. It is important, however, not to overlook the possibility that in spite of strict criteria for choice of cases for treatment, the testicles may descend spontaneously.

As shown in Table I, there are at present in the literature an aggregate of 468 cases of cryptorchidism with 682 undescended testicles which have been treated with gonadotropic substance. Of this number, 286 cases with 431 undescended testicles are shown to have successfully responded to treatment. This is equivalent to 61 per cent of the cases treated and 63 per cent of the associated undescended testicles. On analyzing the literature further, it can be seen that successful results vary, the reports of success ranging between 28 and 100 per cent of the cases treated. Only five of the thirty-one papers reviewed show less than 50 per cent success. Priestly and Cohen[18] (1935) report 25 per cent results; Bigler and associates,[39] 45 per cent; Mimpriss,[32] 30 per cent; Thompson and coworkers,[37] 28 per cent; and in my own report I can claim only 31 per cent successful results. Why there should be such differences in the various series is difficult to explain. It seems to me that the basis for choice of cases is probably the cause. Without a very careful examination or repeated examinations at intervals a number of cases can be unwisely selected for treatment. This is evident frequently in the series reported in the literature. A number of reports show dramatic results following one, two, or even three injections of comparatively small doses of gonadotropic hormone. It would hardly seem logical that such be considered as true cases of cryptorchidism and be reported as yielding successful results. These children would probably have had a spontaneous descent. I feel that if the criteria set forth earlier in this paper were used for each case, the percentage of successful results would, in most series, be fairly parallel.

SUMMARY AND CONCLUSIONS

A summary of the literature on cryptorchidism has been presented in chart form, with an analysis showing that 61 per cent of the cases reported were successfully treated.

Twenty-six cases of cryptorchidism were chosen under strict criteria and were treated with gonadotropic hormone in varying dosage. Eighteen of the cases were unilateral in character, and eight were bilateral.

Complete descent occurred in eight, i.e., 31 per cent of the cases. Of these, five were unilateral and three bilateral.

All patients showed some genital enlargement. In the unsuccessfully treated patients, the testicles and scrotum returned to their original pretreatment size within a period of three to six months after the cessation of injections.

Treatment can be expected to be successful within a period of three months, and generally before 10,000 units of the hormone has been injected.

Massive doses need not be given, and three injections a week are sufficient.

Cases chosen for treatment should fulfill the criteria given earlier in the paper.

Six of the eight successful results were in cases of children below the age of ten. Since this is the case in our findings and since many of the reports in the literature show likewise the most successful results in children under ten, treatment should be seriously considered in the earlier age groups despite the prevailing consensus that treatment should be deferred until the age of ten or eleven.

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498 WEST END AVENUE

CONGENITAL FAMILIAL STEATORRHEA WITH FIBROMATOSIS OF THE PANCREAS AND BRONCHIOLECTASIS

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IN THIS paper we propose to describe what we consider a clinical entity. Because of its apparent familial incidence, its congenital nature, its association with respiratory symptoms, and the post-mortem findings, we suggest the term congenital familial steatorrhea with fibromatosis of the pancreas and bronchiolectasis. In order to differentiate this clinicopathologic complex from the classical celiac disease syndrome, we have attempted to review the past and present concepts of the broad terms "steatorrhea" and the "celiac syndrome" and also to call attention to the hitherto rarely recognized significant association of a respiratory symptom complex with a digestive disturbance. In addition we present our cases.

In medical literature the terms "steatorrhea" and "celiac disease" are closely linked and sometimes used synonymously. It is therefore important to clarify what we mean when we use these terms either alone or qualified, as for example, "congenital steatorrhea," or "pancreatogenous steatorrhea," "idiopathic steatorrhea," or the "celiac syndrome."

The term "steatorrhea" came into prominence when it was employed by Kunzmann[1] to designate the passage of liquid fat with the stools in a case in which he suggested the intimate connection of the phenomenon with disease of the pancreas.

In 1888 Gee[2] applied the term "coeliac affection" to a "chronic indigestion which is met with in persons of all ages, especially in children between the ages of one and five years, in which naked-eye examination of dead bodies throws no light on the nature of the affection. Nothing unnatural can be seen in the stomach, intestines, or other digestive organs." Following this, came a variety of reports by numerous authors, usually describing their cases first as celiac disease, later adding the names intestinal, celiac, or pancreatic infantilism, and pancreatic steatorrhea. Most of their discussions were centered on the controversial subject of etiology, their views depending upon their interpretation of post-mortem findings. Together with this grouping there were also attempts at classification on purely clinical grounds and finally on the basis of laboratory studies.

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Part of this paper was presented by Dr. Benjamin Kramer in a discussion of Dr. H. Andersen's paper "Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease" at the joint meeting of the American Pediatric Society and the Society for Pediatric Research at Great Barrington, Conn., on May 5, 1938.

Thus we have Gibbons,[3] who in 1889 like Gee found that the pathologic anatomy of the celiac affection revealed nothing remarkable and suggested as a cause "a functional derangement of the nervous mechanism involving the digestive glands, with a resulting rapid decomposition of food and absorption into the blood stream of deleterious elements producing ill health."

Herter[4] in 1908 used the term "intestinal infantilism" to designate what was apparently the same condition that Gee had delineated. This author ascribed its origin to an unsuitable intestinal bacterial flora causing excessive putrefaction and chronic intoxication of the neuromuscular system.

The first complete report of a congenital condition in children in which liquid fat which solidified on cooling, passed from the bowel, in contrast to the fatty stools of the celiac affection, was made by Garrod and Hurtley[5] in 1913. Their studies mentioned this feature in two children, one a boy of 8 years, alive, well developed and well nourished, and a brother who died at 11 months of a similar condition which was present from birth. The authors stated that "there were no signs of pancreatic disease, unless it was the steatorrhea," and suggested that the patients were the subjects of a rare inborn error of fat absorption. As no post-mortem examination had been performed on the sibling, the presence or absence of pancreatic pathology remains conjectural. In the fact that the authors failed to mention in their discussion the differential diagnosis from the celiac affection is implied that steatorrhea was a distinct entity not difficult to recognize and totally different from Gee's disease. This difference expresses itself not only in the character of the stools, but in the onset from birth, and in its familial incidence. However, the clinical differentiation of these two groups of cases by subsequent workers was not quite so simple, and their similarities would seem to be much closer than it appears from reading of the early descriptions. It required many years of post-mortem, clinical, and laboratory studies to separate them, not too satisfactorily even to this day.

It was not until 1914 that Poynton, Armstrong, and Nabarro,[6] in studying chronic recurrent diarrheas in childhood, noted in one of their fatal cases a marked increase in the interlobular fibrous tissue of the pancreas. These observers suggested two factors in the etiology of the disease, a possible infection, and the appearance of the celiac affection symptoms as sequelae.

Still[7, 8] in his 1918 Lumleian lectures on celiac disease remarked that the majority of these cases occurred during the latter part of infancy, none ever beginning while the child was breast fed. He attempted to explain the findings of pancreatitis and round-cell infiltration in the intestinal mucosa and submucosa in his case as an inflammatory process secondary to some functional failure of digestive secretion with resulting abnormal decomposition of food residue favoring growth of harmful bacteria.

Miller[9, 10] in 1921 and 1923 reviewed the post-mortem findings of previous cases reported and stated that the intestinal lesions failed to prove that the excessive fat loss in celiac disease was due to enteritis. He argued from the absence of pathologic findings in his own case that the syndrome was independent of organic changes and must be due to a digestive fault, probably a defective action of bile salts on fat absorption. The minor changes in the viscera he attributed to the secondary effects of the fatty diarrhea.

Ryle[11] in 1924 invoked still another idea to explain the possible failure of patients with celiac disease to absorb fat. In two patients operated upon in whom fatty stools were due to faulty absorption, he found obstruction in some parts of the lacteal tree, probably infective in origin. He cited this as one of the possible etiological factors in the disease and considered that improvement when it occurred might be held due in part to the establishment of a collateral lymphatic circulation.

Monerieff and Payne[12] in 1928, referring to the work of Hill and Bloor, indicated that the fat in the feces appeared to have no direct relationship to the fat in the food, but represented some form of excretion of the gastrointestinal tract. They proposed the theory that the primary fault of celiac disease was not a malabsorption of fat, but rather a malutilization, a defect of fat metabolism analogous to defective utilization of sugar in diabetes.

Göttche[13] in 1925 believed that celiac disease might have many causes, the chief of which was dysentery, following which there was a disturbance in carbohydrate metabolism.

As late as 1935, Hess and Saphir,[14] in reporting post-mortem findings in the pancreas in three disputable cases of celiac disease, raised the question whether a difference existed between primary pancreatic disease in infancy and the clinical picture of celiac disease. They stated that, if no changes in the pancreas were found by special staining methods, then it must be conceded that the symptom complex of celiac disease had not one definite pathologic entity. To explain recovery in cases where the pancreatic changes had been the prime factor in the production of clinical symptoms, they cited the ability of the pancreas to regenerate acini and islets of Langerhans.

Excellent clinical presentations of celiac disease were given by Potter[15] in 1926, Lehndorff and Mautner[16] in 1927, Levinsohn[17] in the same year, Fanconi[18] in 1928, and Parsons[19] in 1932. Parsons's brief summary of the chief characteristics of the picture of the fully developed case includes (1) the passage of large, pale, and offensive stools containing considerable amounts of split fat; (2) wasting which may reach a severe degree; (3) abdominal distention; (4) marked stunting of growth amounting to infantilism; (5) anorexia and certain nervous symptoms; and (6) the not infrequent presence of deficiency symptoms.

On the other hand, much investigative work was being done during this time to separate congenital or pancreatogenous steatorrhea from the large group showing the celiac syndrome. Bramwell,[20] in 1915 defined the features of pancreatic infantilism as arrested bodily and sexual development, normal intelligence, no deformity or structural defect of bones, no visceral derangement except chronic diarrhea, flatulent distention of the abdomen, and defective or arrested pancreatic secretion. The latter was shown to be defective or absent by three chemical methods: (1) the presence in the stools of a considerable quantity of undigested fat which decreased after the administration of pancreatic extract; (2) with a milk diet phosphoric acid in the urine was below normal; (3) Sahli's test for the absence of salivary iodine after giving capsules soluble in pancreatic secretion was positive.

Wallis[21] in 1920 thought that the association of positive results in three tests, (1) an increased diastase content of the urine, (2) mydriasis after adrenalin (Loewi's test), and (3) the presence of glycosuria, afforded strong evidence that the pancreas was at fault. If, in addition, creatorrhea and steatorrhea were present, the suspicion of pancreatic insufficiency was confirmed.

However, these points were either not generally known or else not universally accepted. For example Taylor[22] in 1923 grouped celiac disease, celiac infantilism, Herter's infantilism, acholia, pancreatic infantilism, pancreatic insufficiency, and chronic intestinal indigestion as one specific morbid entity. Soecknick and Thoenes[23] in 1927 still tried to rely on a clinical differentiation between celiac disease and pancreatic insufficiency. In the former they found a marked fat loss in the stool, slight protein intolerance, neuropathy, short stature, hydrolability, marked carbohydrate intolerance, and increased peristalsis; in the latter there were "butter stools," marked protein intolerance, no neuropathy or dwarfism, hydrostability, good carbohydrate tolerance, and normal motility of the gastrointestinal tract.

Fanconi[18] in 1928 with the publication of his exhaustive monograph on intestinal infantilism and related forms of chronic digestive disturbances avoided the discussion of the distinctions among the various types of steatorrhea by grouping them under the all-inclusive term of "celiac syndrome." He classified the disorder as (1) the chronic dyspepsias with the celiac syndrome and (2) those without this symptom complex. The former group he divided into a primary and secondary form. The primary group he subdivided into those giving symptoms in the first months of life, as against those with onset in the latter part of infancy, the so-called "Herter infantilism" in the narrower sense. In the secondary group were included those cases associated with ascariasis, marked anemia, and abdominal tuberculosis.

Credit should be given to Parmelee[24] for clarifying the confusion regarding the clinical conditions classified as celiac disease. This he did

by correlating the clinical with the pathologic picture. In 1935 he reviewed the literature and reported two of his own cases of "steatorrhea" which he used in the narrower sense as synonymous with congenital steatorrhea and "pancreatic steatorrhea" for an entity separate from celiac disease. Similarly, in the same year Thaysen[25] summarized his previous work differentiating the steatorrheas of the idiopathic and pancreatogenous types. He grouped celiac disease, nontropical sprue, and tropical sprue as one disease under the designation of idiopathic steatorrhea as opposed to steatorrhea of pancreatic origin. Hanes and McBryde[26] in 1936, in a detailed study of nine instances of the sprue syndrome, found this classification satisfactory. Thaysen expressed the belief that the clinical picture might be similar in all types, but felt that certain metabolic disturbances were pathognomonic of idiopathic steatorrhea, namely, (1) an abnormal secretion of fat in the feces; (2) normal or very slightly raised fecal nitrogen; (3) a flat blood sugar tolerance curve; and finally (4) an increased basal metabolic rate. Figures of total fat in the feces with respect to amounts of neutral fat, soaps, and free fatty acids were of no practical interest. Moreover, an exactly corresponding splitting of fecal fats into free fatty acids and soaps is found in pancreatic as in idiopathic steatorrhea, a phenomenon that is explicable by the lipolytic action of the intestinal secretion itself, as stressed by Leathes and Raper.[27]

In refutation of Payne and Moncrieff's work, Thaysen and his collaborators found that steatorrhea is due to a diminished fat absorption and not to an excretion of fat by the intestines. Because patients with pancreatic steatorrhea may have a normal blood sugar tolerance curve, the pathognomonic feature of this disease is the finding of an excessive nitrogen excretion in the feces.

Harper,[28] in 1938 presented eight cases of congenital steatorrhea due to pancreatic defect, five* with post-mortem findings. She reviewed several more cases previously reported by other authors as celiac disease in which pathologic changes in the pancreas were present. She also added a chart of a differential diagnosis between congenital pancreatic steatorrhea and celiac disease. In this were included (1) the symptoms present from birth, (2) the "butter stools," (3) high fecal fat with large amount of unsplit fat, (4) glucose tolerance test on the high side of normal, (5) and post-mortem lesions found in the pancreas in congenital steatorrhea, as opposed to the (1) onset from nine months to two years, (2) oil not present in the stools, (3) high fecal fat well split, (4) flat glucose tolerance curve, and (5) absence of lesions in the pancreas in celiac disease. The signs of failure to absorb fat, namely, emaciation, meteorism, anemia, and osteoporosis, were common to both.

With this preliminary summary we are presenting two cases in one family, with autopsy findings in one, in which the interpretation of the complete picture and the diagnosis in both was made in retrospect.

*Harper reported 4 cases with post-mortem findings and subsequently added the fifth.

REPORT OF CASES

CASE 1.—N. H., a 7-month-old white female, was admitted to the Jewish Hospital of Brooklyn on April 15, 1936, because of wheezing, cough, large foul smelling stools, and failure to gain weight.

Family History.—The patient was the second child of healthy parents, mother 26 years old, father 21 years old; there was no consanguinity. There had been one other child, a 2-year-old brother to the patient, who, too, had presented a feeding problem since birth and was under treatment for celiac disease.

Past History.—The patient was born at full term; delivery was normal and spontaneous; weight, 6 pounds, 15 ounces (3,150 gm.). She had presented a feeding problem since birth and had always had several large slimy foul smelling stools daily. She had been fed various dilutions of milk and water with added dextrimaltose. Viosterol and orange juice were begun at one month, bananas and egg yolk at five months. Cereals and cow's milk did not agree with her. Since the age of 2 months, the patient had been wheezing. She was seen at 2½ months because of failure to gain weight and the presence of large stools. She appeared undernourished and poorly developed. The heart and lungs were normal. The abdomen was protuberant; the wall showed poor muscle tone; the liver and spleen were not palpable. The extremities were thin, and there was a sparse amount of subcutaneous fat. She was placed on an evaporated milk formula. She was seen again at 4½ months, and during this interval her formula had been changed frequently to include lactic acid milk, and protein milk with banana powder. Her wheezing became more noticeable; her weight was stationary. The stools were large, frothy, and foul smelling. At 6½ months the patient developed a croupy cough, and numerous rhonchi were audible in both lungs. The temperature varied between 101 and 102° F. for one week. The wheezing grew progressively worse. There was a loss of weight and at 7 months the patient weighed 11 pounds (5,000 gm.). Occasional attacks of cyanosis appeared, and, because of these together with fever, dyspnea, and a nonproductive cough, the patient was brought to the hospital.

Physical Examination.—On admission she appeared acutely ill, dyspneic, cyanotic, showing movement of the alae nasi. Wheezing and marked retraction of the sternum were prominent features. The temperature was 101° F. and the respirations, 68 per minute. The head measured 39.3 cm. in circumference. The anterior fontanel was 2 by 2 cm., and the posterior fontanel was closed. The pupils reacted to light and to accommodation. The eardrums were normal. There was a moderate amount of grayish discharge from the nose. The lips were cyanotic, the tongue was coated, and the pharynx was deeply injected. The chest presented diminished resonance over the upper lobes anteriorly, with scattered coarse, moist râles throughout the entire chest. The heart was not enlarged, and auscultation revealed no murmurs. The abdomen was distended and flabby; the liver and spleen were not palpable. The extremities were negative. The clinical impression was bronchopneumonia and celiac disease.

Laboratory Data.—Urinalysis on admission showed a trace of sugar. Blood study showed the following: hemoglobin, 84 per cent; red blood cells, 5.5 million; white blood cells, 20,400, with 67 per cent polymorphonuclear leucocytes, 27 per cent lymphocytes, 4 per cent mononuclears, 1 per cent eosinophiles, and 1 per cent myelocytes. The red cells were normal in appearance and the platelets adequate in number. Laryngeal culture yielded pneumococcus Type IX. Tuberculin test was negative to 0.1 mg. Roentgen study of the chest showed a generalized mottling of each lung field, suggesting the presence of bronchopneumonic infiltration.

Course in the Hospital.—The patient was placed in an oxygen tent where the cyanotic attacks persisted. The cough became paroxysmal and its character suggestive of pertussis. Adrenalin was ineffectual. Because the attacks of cyanosis followed shortly after feeding of diluted cow's milk, evaporated milk was substituted to rule

out the possibility of an allergic factor, to no avail; protein milk feedings were without effect. On April 18 the stools were large, numerous, slimy, and foul smelling. On the following day the infant became stuporous, the abdomen distended, and the liver palpable. Dyspnea and cyanosis were marked. Everywhere in the chest were medium fine râles; no dullness was present. The temperature rose to 104° F., and after five days of hospitalization the patient expired. The final diagnosis was bronchopneumonia, celiac disease.

NECROPSY REPORT

Gross Examination.—The body was poorly developed and poorly nourished. The skin was not unusual; there was no superficial adenopathy or dependent edema. The head was well formed. The pupils were equal and regular and the sclerae were not unusual. There was a slight yellow mucoid discharge from the nostrils and from the mouth. The mucous membranes of the lips and mouth as well as the nail beds were cyanotic. The chest was symmetrical. The abdomen was rounded and tensely distended. The external genitals and the extremities were normal. There was about 0.5 cm. of adipose tissue in the midline of the anterior abdominal wall. The serous cavities showed no excess fluid, and the lining surfaces were smooth and glistening. The intestines were distended. The inferior margin of the liver extended 2 cm. below the costal margin in the right midclavicular line. The lungs were voluminous. The thymus measured 7 by 4 by 1 cm. and weighed 12 gm. The transverse diameter of the heart measured 7 cm., that of the chest, 12 cm.

Heart.—The heart measured 5.5 cm. from apex to base and 4.5 cm. at the base. The epicardium was smooth and glistening. The endocardium of the right atrium was smooth, the musculi pectinati were well formed, and the interstices between them were of average depth. The atrioventricular orifice measured 5.5 cm. in circumference; the valve leaflets were delicate. The right ventricle measured 2 mm. in thickness. The pulmonary orifice was 2.8 cm. in circumference, and the cusps were delicate. The ductus arteriosus was closed. The left atrium was lined by smooth endocardium. The atrioventricular orifice measured 4 cm. in circumference. The valves were delicate, the chordae tendineae were velamentous and inserted beyond the free edges of the cusps; the trabeculae carneae were well rounded. The foramen ovale was patent. The wall of the left ventricle measured 8 mm. in thickness. The aortic orifice measured 2.5 cm. in circumference; the cusps were thin and delicate. The coronary ostia were patent. The heart weighed 35 gm.

Lungs.—The external surfaces were smooth and shiny. There were a few petechial hemorrhages beneath the pleurae. The cut surfaces were uniformly pink. The bronchi and bronchioles were prominent, and their walls were thickened. Some of them were dilated and exuded thick yellow-green pus. The right and left lungs weighed 76 and 86 gm., respectively. The mucosae of the trachea and bronchi were opaque and red, and their lumina were filled with yellow green thick material.

Spleen.—The spleen weighed 18 gm. and held its shape well. The external surface was smooth and purplish red. On the cut surfaces the Malpighian bodies were distinct, and the fibrous markings were not increased.

Stomach and Intestines.—The stomach was distended with about 75 c.c. of semisolid gray material. The mucosa was smooth, intact, and pink. The duodenum was lined by smooth, pink mucosa. The mucosa of the jejunum and ileum was not unusual.

Liver and Gall Bladder.—The liver weighed 240 gm. The peritoneal surfaces were smooth and shiny. The cut surfaces were pale yellow-brown and had a fatty consistency. The liver markings were somewhat indistinct. The gall bladder was not unusual on its external or cut surfaces.

Pancreas.—The pancreas measured 7 cm. in length and weighed 8 gm. It was firm and pale. The cut surfaces showed the usual lobulation.

Suprarenal Glands.—Both glands together weighed 10 gm. Cortex and medulla were well demarcated.

Kidneys.—The right and left kidneys weighed 28 and 22 gm., respectively. The capsule stripped readily, revealing a smooth red-brown surface with occasional fetal lobulation. On the cut surface the cortex and medulla were well demarcated, and the cortex measured 4 mm. in thickness. The pelvic mucosa was smooth, intact and pink.

Pelvic Organs.—There was nothing unusual about the rectum, bladder, Fallopian tubes, and ovaries.

Blood Vessels.—The aorta was elastic and its wall thin. There were no atheromatous patches anywhere on the intimal surface. There were no vascular anomalies.

Lymph Nodes.—The mesenteric lymph nodes were not enlarged. The hilar lymph nodes were enlarged. On section they were uniformly brown red and succulent.

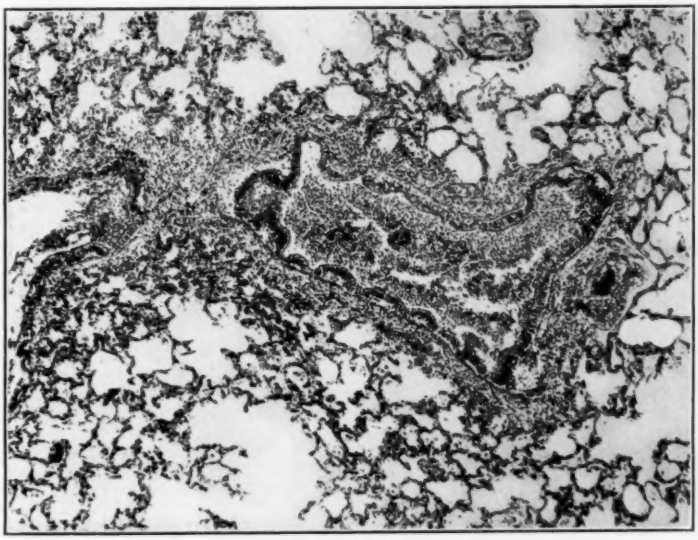

Fig. 1.—Case 1. Photomicrograph of a lung showing bronchiolectasis and bronchopneumonia. Note lumen of bronchiole distended with purulent exudate which infiltrates the wall and fills the surrounding alveoli. Several areas of compensatory emphysema are also present. Hematoxylin and eosin, ×85.

Microscopic Examination

Thymus.—The cortical and medullary zones were well demarcated. In the latter the Hassall's corpuscles were numerous. The interlobular connective tissue was delicate.

Heart.—The myocardial fibers were well preserved, with distinct striations and well-stained nuclei.

Lungs.—The bronchi and bronchioles were dilated and filled with a fibrinopurulent exudate which adhered to the wall where the mucosa was missing. The wall was thickened by edema and infiltrated with polymorphonuclear leucocytes. The capillaries were distended with blood. The surrounding alveoli contained a similar exudate, and their walls were similarly thickened. The connective tissue about the larger vessels also contained many polymorphonuclear leucocytes. The intervening alveoli were either empty, somewhat emphysematous, or contained a fibrinopurulent exudate. The trachea showed no evidence of epithelial metaplasia.

Spleen.—The capsule and connective tissue septa were delicate. The Malpighian bodies were numerous and well spaced. The splenic pulp was congested.

Liver.—The capsule was delicate and the arrangement of the liver cords into lobules was orderly. The veins and sinusoids were distended with blood. The cytoplasm of the liver cells was coarsely granular and in places markedly vacuolated.

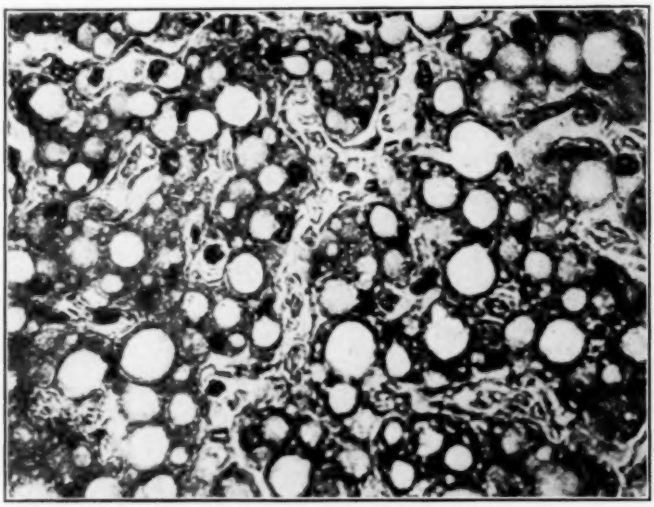

Fig. 2.—Case 1. Photomicrograph showing marked vacuolization of liver cells and disturbance in the normal cytoarchitecture. Hematoxylin and eosin, ×100.

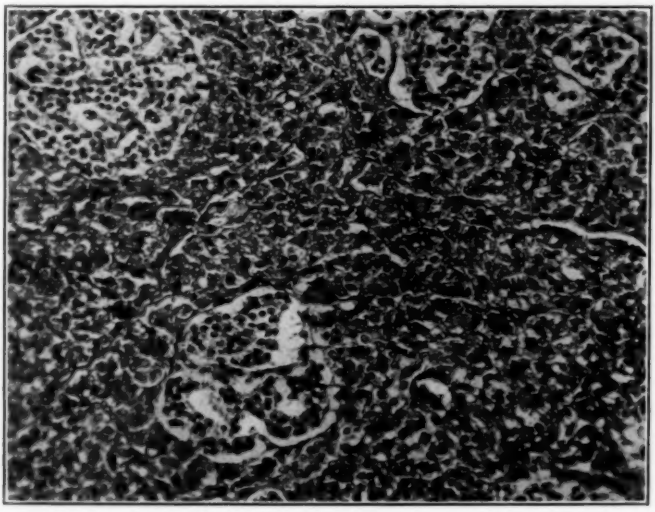

Fig. 3.—Case 1. Photomicrograph of a normal pancreas showing uniform arrangement of well-stained acini between which thin strands of fibrous tissue and occasional delicate capillaries are noted. The islets of Langerhans are well preserved. Hematoxylin and eosin, ×275.

In sections stained with sudan III, these were filled with golden brown staining material. The periportal spaces were not remarkable. There was no apparent increase of fibrous connective tissue, and no cellular infiltration.

Pancreas.—There was a marked increase of intralobular and interlobular fibrous connective tissue. The normal cytoarchitecture was markedly altered. The islets of Langerhans were large and unevenly distributed, the acini were relatively scant. The ducts were numerous and distended, but not obstructed; the lumina of many were filled with a homogenous pink staining material. The lining cells of the ducts were well preserved. There was a slight infiltration of the connective tissue with small round cells and large mononuclear cells.

Suprarenal Glands.—There was nothing unusual, the cells were well preserved.

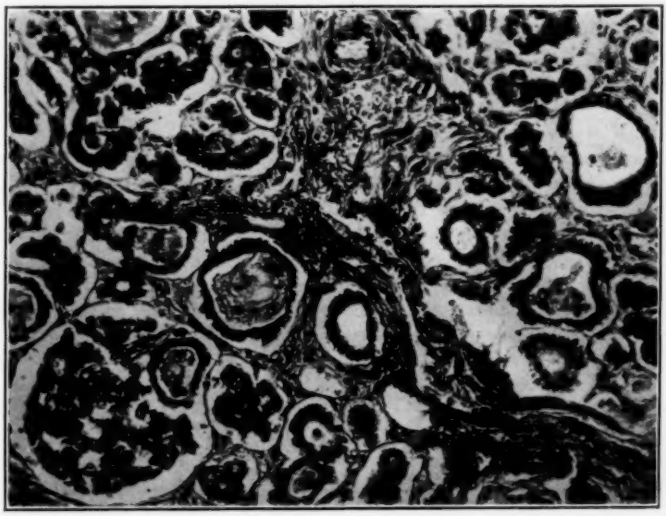

Fig. 4.—Case 1. Photomicrograph of pancreas showing irregularly spaced and dilated acini lined by flat to cuboidal cells. The lumina contain an amorphous pink-staining material. Between the acini broad bands of thick connective tissue with an occasional thin-walled blood vessel are noted. These extend throughout the tissue, and in places contain foci of small mononuclear cells. The islets of Langerhans are well preserved and somewhat larger than normal. Hematoxylin and eosin, ×275.

Kidneys.—The glomeruli were numerous and fairly well spaced; the capillaries were dilated with blood. The convoluted tubules showed varying degrees of cloudy swelling of their lining cells. The collecting tubules were lined by well-preserved cells. There was no cellular infiltration and no increase of the interstitial connective tissue. The urothelium of the pelvic mucosa was well preserved, showing no metaplasia.

Pelvic Organs, Intestines, Blood Vessels, and Lymph Nodes were not abnormal.

Post-Mortem Culture from Lung.—Staphylococcus aureus and *H. influenzae.*

Anatomical Diagnosis.—Tracheitis, bronchitis; acute bronchiolitis; bronchiolectasis; focal pneumonia (bilateral); fibrosis of pancreas; fatty changes of the liver.

CASE 2.—J. H., 2½-year-old white male, brother of patient in Case 1, was admitted to the Jewish Hospital of Brooklyn on July 2, 1936, because of cough, dyspnea, and nasal discharge.

Past History.—The patient was born at full term; delivery was normal and spontaneous; birth weight, 7 pounds, 8 ounces (3,400 gm.). There was no cyanosis or convulsion. He was breast fed for five weeks and showed no gain in weight; subsequently various formulas were tried. There was a persistent nonspasmodic and nonproductive cough since birth, and during the neonatal period the possibility of the infant's having a congenital cardiac anomaly was entertained. No murmur was ever heard. There was no fever and no vomiting. There were from four to six fairly large bowel movements daily, some foul smelling, and others watery. At the age of 9 weeks the patient's cough became more severe and paroxysmal, so that pertussis was suspected. There were, however, neither whoops nor emeses. The patient, when seen again at the age of 3 months, weighed 8 pounds (3,640 gm.). He was placed on a lactic acid-evaporated milk formula with karo syrup, and pablum. At 7 months of age he weighed 17.6 pounds (8,000 gm.). He was subject to frequent upper respiratory infections and a persistent nonspasmodic cough. The stools were occasionally watery and foul. At 9 months of age the patient appeared fairly well developed and well nourished, but his weight remained stationary. He was 27.2 inches (69 cm.) tall. The anterior fontanel measured 3 by 2 cm., and there was no evidence of rickets. The tissue turgor was good. The chest and heart showed nothing unusual. The abdomen was distended, and the liver 3.5 cm. below the right costal margin. Vegetables and egg yolk were added to the diet. At 13 months of age the patient weighed 19.8 pounds (9,000 gm.) and was 30 inches (76 cm.) tall. Cereal, vegetables, egg yolk, bananas, and cheese were well tolerated, as well as the evaporated lactic acid milk formula. The bowel movements were large, particularly those in the morning. On examination prominent frontal and parietal bosses were found. The anterior fontanel admitted one finger. There was no costochondral enlargement. The chest and heart showed nothing unusual. The abdomen was distended, the liver palpable 1 cm. below the costal margin. At 16 months the patient weighed 19.5 pounds (8,860 gm.) and was 30 inches (76 cm.) tall. He had been on re-enforced protein milk for the preceding five weeks, in addition to banana, cheese, egg yolk, liver, fish, and steak. The diet was well tolerated and his appetite was good. He had about three large stools daily. Roentgen ray studies of the bones showed nothing unusual. On examination the abdomen was still markedly distended with the liver edge at the costal border. Hypogenitalism was prominent, and there was bilateral cryptorchidism. The heart was normal and there was no craniotabes. At 21 months of age the patient weighed 22.7 pounds (10,320 gm.). The bowel movements were still large, and the abdomen was protuberant. The patient was receiving buttermilk, cottage cheese, bananas, eggs, liver, lamb chops, chicken steak, apple sauce, and jello. Viosterol and orange juice were continued. At 25 months of age the patient had been doing well except for frequent upper respiratory infections consisting of cough and running nose. There was no vomiting, no fever, no diarrhea. The stools were large and foul smelling. He weighed 25.12 pounds (11,440 gm.) and was 33.25 inches (84.5 cm.) tall. On examination there were no new findings.

Present Illness.—About a week prior to admission the patient developed a watery nasal discharge and severe cough. He was not acutely ill, and the course was afebrile until two days before entry, when the temperature rose to 101° F. On the day of admission he appeared cyanotic and dyspneic.

Physical Examination.—On admission he appeared fairly well developed and well nourished, acutely ill, dyspneic and cyanotic. The temperature was 101.6° F., pulse 114, and the respirations 32 per minute. There was moderate retraction of the lower anterior chest. The head was normal. The pupils were equal and regular and reacted to light and accommodation. The eardrums were normal. There was a watery nasal discharge, and the nasal mucosa was red and edematous. The lips were

cyanotic; the throat was moderately inflamed. There was no cervical lymphadenopathy and no nuchal rigidity. The lungs revealed impaired breath sounds over the lower lobes posteriorly; sibilant and subcrepitant râles were heard throughout the chest. The heart was not enlarged, and there were no murmurs. The abdomen was distended and soft; liver and spleen were not palpable. Hypogenitalism was evident. The extremities were normal. The clinical impression was acute tracheobronchitis, bronchopneumonia, and celiac disease.

Laboratory Data.—Urinalysis showed nothing unusual. On July 4 the hemoglobin was 80 per cent; red blood cells, 4.5 million; white blood cells, 13,000; polymorphonuclear leucocytes, 70 per cent; band forms, 5 per cent, and lymphocytes 25 per cent. The red cells were normal in appearance and the platelets, adequate in number. On July 12 the hemoglobin was 80 per cent, the red blood cells, 4.1 million; white blood cells, 18,700, 72 per cent polymorphonuclears, 1 per cent basophiles, 4 per cent mononuclear cells, and 19 per cent lymphocytes. On July 21 the hemoglobin was 70 per cent, red blood cells 4.7 million. Throat culture revealed few hemolytic streptococci. Cough plate showed no *H. pertussis*, sputum culture yielded *Staphylococcus aureus* and *B. subtilis*. Mouse culture of sputum revealed streptococcus hemolyticus. Guinea pig inoculation for tuberculosis was negative. Agglutinations for typhoid, melitensis, and tularemia were negative. Mantoux tests with O. T. and avian tuberculin were negative. Roentgen studies of the chest on July 2 showed considerable bilateral root enlargement and exaggerated bronchovesicular markings. No parenchymal lesions or superior mediastinal tumor were demonstrated. Repeated studies on July 7 showed no additional findings. On July 14 considerable root and perivascular infiltration was observed bilaterally. The bronchial tree was thickened in a fanlike fashion from the root almost to the periphery of the lung, and the findings seemed to indicate a hilar adenitis and periadenitis with bronchial irritation. The intercostal spaces were slightly wider than average, and the diaphragm was depressed, suggesting some degree of emphysema.

Course in Hospital.—The patient was placed on a buttermilk, cheese, dextrimaltose formula. He also received puréed vegetables, chicken liver, banana, egg yolk, jello, junket, and 4 ounces of orange juice a day. Tincture of benzoin inhalations were begun soon after admission and ephedrine sulphate gr. $\frac{1}{8}$ and atropine gr. $\frac{1}{500}$ were administered. On July 3 the temperature ranged between 99 and 100.6° F. In view of the bilateral hilar shadow, radiotherapy was suggested, and the patient received one treatment to the chest. He refused to eat and tolerated only small quantities of the formula. The stools were clay colored and pasty. On July 4 the temperature ranged about 101° F. The patient was seized with attacks of repeated coughing and cyanosis, paroxyms that simulated very much those seen in severe pertussis, except that no whoops or emeses followed them. Marked dyspnea and retraction of the lower chest were noted. On July 6 the cyanosis persisted, and respirations were chiefly abdominal in type; the intercostal spaces were drawn inward at the diaphragmatic attachment. He was given tincture of belladonna and appeared more comfortable. He took his feedings well and had no diarrhea. On July 7 the respirations were 52 per minute, and the temperature was 104° F. Cyanosis of the lips and nail beds with increased retraction of the lower chest was noted; moist râles were heard throughout the chest. He was placed in an oxygen tent for a few hours and then in a respirator. The latter had no good effect, and after twenty minutes he was returned to the oxygen tent. From July 10 on the respirations became labored with increasing retraction of the chest, and in addition suprasternal and supraclavicular retractions appeared. Cyanosis of the lips was persistent. Temperature ranged between 100 and 101° F. Periods of marked dyspnea were relieved by intermittent doses of adrenalin. An area of suppressed bronchial breathing appeared at the left base. The clinical course was suggestive of asphyxia resulting from extensive

bronchial and peribronchial inflammatory involvement. The physical signs indicated some confluence of the exudate at the left base giving rise to an area of consolidation. On July 16 the patient's condition was poor. Breathing had been labored, for the most part, with cyanosis aggravated by spells of coughing during which the patient brought up masses of tenacious mucopurulent material. Breath sounds were absent throughout the chest and occasional moist râles were heard posteriorly. There were varying periods of stupor; the pulse was at times imperceptible. The abdomen was moderately distended and the liver was palpable, 3 cm. below the costal margin. There was a striking absence of toxemia that one would expect with any pneumonia, especially one so widespread and accompanied by so much exudation. Whatever toxicity seemed to be present was anoxemic rather than bacterial. On July 18, 19, and 20 the patient experienced severe attacks of dyspnea and cyanosis requiring adrenalin and caffeine sodium benzoate. Several small direct blood transfusions had been given. On July 21 the patient's condition was very poor. The skin and mucosae were cyanotic. The chest revealed absent breath sounds and scattered râles. The heart sounds were feeble and rapid. The abdomen was markedly distended; the liver was 5 cm. below the costal margin. There was no peripheral edema. The patient died on July 22. The final diagnosis was bronchopneumonia and celiac disease. Consent for an autopsy could not be obtained.

COMMENT

The histories of the two cases are almost identical, and the probability is that the underlying morbid anatomy was not different. The most striking changes were revealed in the pancreas and lungs in Case 1, which came to autopsy. Considering the pancreas, we note similar or closely related findings in previously reported cases with histories suggesting celiac disease. As already mentioned, the cases of Poynton, Armstrong, and Nabarro,[6] reported in 1914, showed increase in interlobular fibrous connective tissue, particularly that surrounding the ducts. This was in a 9-year-old child with a chronic recurrent diarrhea.

In Still's case[8] the findings suggested a pancreatitis, but the appearance was similar to that of Poynton's case. Passini[29] in 1919 found in one patient aged 9 months a small pancreas with cystic changes in the acini and a reduction in the number of islands of Langerhans, and in a 2-month-old sister a similar picture. Another infant of 18 months showed widening of the pancreatic ducts and a necrotic parenchyma. All three cases had been treated without success with the usual celiac disease regime. Schick and Wagner[30] in 1923 reported in a 17-month-old child atrophy of the pancreas in addition to atrophy of other digestive glands and organs of internal secretion. Clarke and Hadfield[31] in 1924, in a child of four years, found more than one-half of the pancreas to be fibrous tissue with no evidence of active inflammation and no cellular infiltration between lobules. The islands of Langerhans showed no pathology and were relatively increased in number over acini.

Mautner[32] in 1925 demonstrated in a 3-year-old child a pancreas with marked degeneration of the exocrine apparatus with alveoli distended and filled with eosin red secretion, and an intact islet mechanism.

Burghard[33] in the same year presented an infant of 10 months with cystic degeneration of the pancreas and an increase in the interlobular connective tissue.

Gross[34] in 1926 described a 15-week-old infant clinically and pathologically resembling Burghard's[33] and Passini's[29] cases and another 19-month-old child with a clinical picture of celiac disease, whose pancreas showed marked atrophy and fatty infiltration of the secreting parenchyma and only slight involvement of a relatively increased number of islands.

Siwe[35] in 1932 described a 2-year-old child, with well-preserved islets of Langerhans in contrast to an almost total agenesis of the exocrine portion of the gland.

Huet's case,[36] a 10-year-old boy, reported in 1933, showed similar findings.

Greenberg[37] in 1933 refers to an unreported case of an 11-month-old infant in whom a completely fibrotic pancreas was found.

Hess and Saphir[14] in 1935 described two cases, 9 and 18 months of age, showing "chronic pancreatitis," much fibrosis, concrements in dilated ducts, and seemingly large islands of Langerhans; and a third child of 3 years with fibrosis of the pancreas, with very few inflammatory cells, suggesting subsidence of the active process.

Parmelee[24] in 1935 reported two cases, one 11 years old, the other 4½ years old, both of whom displayed in the pancreas marked fibrosis, a great reduction in the amount of secretory gland tissue, large islands of Langerhans, and dilatation of the pancreatic ducts.

The cases of Fanconi, Uehlinger, and Knauer,[38] aged 3 years and 10 months, respectively, reported in 1936 duplicate the ones described by us.

Garesche,[39] in 1936 in addition to quoting a case of Freudenberg's, of a one-year-old infant, mentioned one case of his own, a child of 4 years, with changes in the pancreas similar to those described by Parmelee and Fanconi.

Harper[28] in 1938, in her report of eight cases of congenital steatorrhea, presented post-mortem findings in five. One showed tuberculosis of all the organs with fatty replacement of atrophied pancreatic tissue; the other four had small distorted pancreatic acini with increased stroma. In one of these distended pancreatic ducts were present.

Lucksch and Sachs[40] in 1937 reported a case of questionable indigenous sprue in a 24-year-old female in whom atrophy of the pancreas was found.

Whereas all of these cases showed fatty degeneration or atrophy of the secreting parenchyma, accompanied as a rule by interstitial fibrosis, in most instances the islets of Langerhans either remained intact or were increased in size, or relatively, in number. This is a sharp contrast to the findings in 1914 of Nakamura,[41] and in 1926 of Dreyfuss,[42] who, in systematic studies of the pancreas in cases of ordinary metabolic dis-

turbances not resembling the celiac syndrome, found frequent involvement of the islet cells with the acini spared.

A review of the reported cases in the literature leaves the impression that the steatorrheas, excluding the acquired forms in adults of pancreatic inflammation or lithiasis, or those in which pathology of the lacteals is found, may be divided into idiopathic and pancreatogenous forms. The former includes celiac disease and sprue, tropical and nontropical. All of these may show the clinical picture of the celiac syndrome, namely large, pale, offensive, fatty stools, abdominal distention, anorexia, wasting, stunting of growth, and the presence of deficiency symptoms such as rickets, tetany, scurvy, edema, xerophthalmia, osteoporosis, and anemia. The differentiation between them rests chiefly on the finding of a high nitrogenous excretion in the feces in the pancreatogenous form. Sugar tolerance curves may be of value, being usually of the diabetic type in the pancreatogenous steatorrheas in contrast to the low, flat curve in the idiopathic form. Of some importance, too, is the onset of the pancreatic type almost from birth. The final differential diagnosis is based on post-mortem findings, where no lesions are seen in the pancreas of idiopathic steatorrhea, in contrast to the striking and often characteristic changes detected in the pancreatogenous group.

The association of the respiratory symptoms with steatorrhea has been stressed by many authors; most of whom considered the former the result of an intercurrent infection. Lehndorff and Mautner,[16] for example, in their comprehensive summary of celiac disease in 1927, called attention to the not infrequent affection of the bronchial passages as responsible for fever. Fanconi[18] in 1934, in discussing the various groups of "dormant" pneumonias in childhood, described six cases of the association of chronic pneumonias with marked chronic dyspepsia. Later, in 1936, this author, together with Uehlinger and Knauer,[38] was afforded the opportunity of examining all the organs in two children with chronic bronchitis, who had developed "celiac disease" soon after birth. They ascribed a definite cause for this, namely, a congenital bronchiectasis. Although not the first to describe the concomitant occurrence of these two conditions in the same case, they were responsible for pointing out their association as congenital anomalies. They preferred to look upon these two sets of symptoms as resting independently on a common basis rather than speaking of the celiac syndrome and bronchiectasis in a cause and effect relationship. However, while Fanconi and his co-workers[38] described their cases under the heading of celiac syndrome, we believe that they belong in the grouping of pancreatogenous steatorrhea.

Cockayne[43] in 1933 had discussed the high mortality in steatorrhea and the frequency with which pneumonia was the cause of death. Harper[28] in her 1938 series was of the opinion that this association was more than a coincidence, but she ascribed it to a greatly reduced resistance to respiratory infections. It is interesting to note that in other patients

with steatorrhea dying of broncho-pneumonia, the latter feature is mentioned casually as contributing to the death of the patient, and in most instances, no great detail as to the character of pulmonary parenchymal and bronchial involvement is given. Among these are Poynton, Armstrong and Nabarro's two patients (Cases 5 and 6) suffering from frequent attacks of bronchitis, and the patients dying of bronchopneumonia reported by Passini[29] and Pipping,[44] Mautner,[32] Soecknick and Thoenes.[23] Clarke and Hadfield's patient,[31] supposed to have died of an intercurrent infection, showed in the lungs small abscess cavities with recent ulceration of the walls, and pus in the large bronchi. Burghard's case[33] revealed fresh lobular pneumonia and purulent catarrhal bronchitis. Two cases of Gross,[34] had had chronic bronchitis or pneumonia. Siwe's patient[35] died of a bronchiolitis after several bouts of bronchitis. The patient described by Huet[36] had had a chronic lung infection, and at post-mortem there was demonstrated a diffuse bronchopneumonia, widened bronchi, and bronchioles surrounded with thickened walls. Similarly in Parmelee's two cases[24] chronic bronchitis and bronchopneumonia had been prominent features in their long illnesses with the revelation of a purulent bronchitis and bronchiolitis at necropsy. One of the cases of Hess and Saphir[14] displayed a bilateral bronchopneumonia with abscess formation, while in the other two bronchopneumonia was demonstrated. Garsche's own patient,[39] and that of Freudenberg,[45] quoted by the former, had died of "grippal" pneumonia. In Lucksch and Sachs's patient,[40] an adult, a bilateral lobular pneumonia was found at autopsy. Another adult, still alive at the time of publication, is the patient having "chronic idiopathic steatorrhea with asthmatiform bronchiectasic bronchitis" reported by Campanacci[46] in 1937.

Table I is a summary of the cases of steatorrhea associated with respiratory symptoms recorded in the literature to date, including our own.

Among all these cases the ones most closely resembling those reported by us as congenital familial steatorrhea with fibromatosis of the pancreas and bronchiolectasis are those of Fanconi, Uehlinger and Knauer.[38] These had in common the onset from birth, the similar clinical course and autopsy findings, and in their Case 2, the familial incidence. Probably similar cases except for the positive familial history may be found in the previously discussed papers of Parmelee,[24] Huet,[36] Burghard,[33] Hess and Saphir,[14] and possibly Campanacci.[46]

Possibly closely related, but incomplete because of lack of details in history or necropsy findings, may be the cases of Poynton and his colleagues,[6] Still,[8] Clarke and Hadfield,[31] Pipping,[44] Passini,[29] Gross,[34] Harper,[28] Soecknick and Thoenes,[23] Siwe,[35] Garsche,[39] Mautner,[32] and Lucksch and Sachs[40] in an adult.

There is ample evidence in embryology and pathology for the support of the theory of the independence of the respiratory and intestinal symp-

TABLE

SUMMARY OF CASES OF STEATORRHEA

NO.	YEAR	AUTHOR	TITLE OF REPORT (ENGLISH TRANSLATION WHERE INDICATED)	CHIEF SYMPTOMS OR SIGNS APPROXIMATE AGE OF ONSET		FAMILY INCIDENCE
				INTESTINAL	RESPIRATORY	
1	1914	Poynton Armstrong and Nabarro	Chronic recurrent diarrhea in childhood	Enteritis from 12th to 20th month	None	One sibling died of diarrhea as an infant
2	1918	Still	Celiac disease	Loose stools for 4 months beginning at 7 years	None	None
3	1919	Passini	Pancreatic disease as the cause of children's failure to thrive	Thin stools since birth	Bronchopneumonia at 9 mo.	One sibling of two months with similar condition
4	1919	Passini	Same	Thin stools since birth	Bronchopneumonia and empyema at 2 mo.	Sister of Case 3 above
5	1919	Passini	Same	Loose stools	Bronchopneumonia at 18 mo.	None
6	1924	Clarke and Hadfield	Congenital pancreatic disease with infantilism	Fatty diarrhea since birth; underweight and undersized	Intercurrent infection bronchopneumonia 7 weeks after admission	None
7	1924	Pipping	Contribution to knowledge of Herter's intestinal infantilism	Gastrointestinal difficulties at 2 years	Recurrent bronchopneumonia from 2nd to 7th year	1 brother, "weak stomach"; 1 sister 3 mo. gastrointestinal disturbances; recurrent bronchopneumonia
8	1925	Mautner	The Heuter-Heubner digestive insufficiency	Recurrent diarrhea beginning at 1 yr.	Pneumonia at 3 yr.	None

I

ASSOCIATED WITH RESPIRATORY SYMPTOMS

OUTCOME AND MANNER OF TERMINATION	POST-MORTEM FINDINGS			REMARKS
	PANCREAS	LUNGS	LIVER	
Died at 9 yr. after operation for suspected peritonitis, not found	Interlobular fibrosis especially surrounding ducts	Not reported	Pale, soft: fatty changes	None
Died of exhaustion. Suspected diagnosis of tuberculous peritonitis at 7½ yr.	Excess of fibrous tissue, especially about ducts, suggestive of pancreatitis.	Not reported	Small and congested	Tests made for pancreatic insufficiency during life were negative (Sahli test)
Died of bronchopneumonia at 9 mo.	Pancreas one-half normal size; cystic changes in acini; reduction in number of islands of Langerhans	Not reported	Not reported	Details of respiratory symptoms and pulmonary findings not given
Died at 2 mo. of bronchopneumonia and empyema	Cystic degeneration of pancreatic glands; atrophy of islets of Langerhans	Bronchopneumonia and empyema	Not reported	No details of respiratory symptoms and pulmonary findings
Died at 18 mo. of bronchopneumonia	Necrotic parenchyma; pancreatic ducts distended by secretion	Bronchopneumonia	Not reported	Details not given
Died at 4 yr. of bronchopneumonia	Shrunken, dead white, fatty; $\frac{1}{20}$ the normal amount of secretory glandular tissue; replacement fibrosis; no evidence of active inflammation; islands normal	Terminal bronchopneumonia; small abscess cavities; pus expressed from large bronchi	Fatty changes extreme	One sibling died at 2½ mo. from bronchopneumonia; one at 2½ yr. from post-pertussis pneumonia
Died of bronchopneumonia at 7 yr.	Not described	Bronchopneumonia	Fatty infiltration	Fever of unknown etiology 5 weeks before onset of gastrointestinal symptoms
Died at 3 years of pneumonia	High grade degeneration of exocrine apparatus; alveoli distended and filled with eosin-red secretion; intact islands of Langerhans	Acute lobular pneumonia with beginning pleural effusion	Enormous fatty liver	Impossible to demonstrate primary insufficiency of pancreas during life

TABLE I

NO.	YEAR	AUTHOR	TITLE OF REPORT (ENGLISH TRANSLATION WHERE INDICATED)	CHIEF SYMPTOMS OR SIGNS APPROXIMATE AGE OF ONSET		FAMILY INCIDENCE
				INTESTINAL	RESPIRATORY	
9	1925	Burghard	Pancreatic disease of infancy	From birth 4 loose, large, foamy, foul-smelling stools daily	Paroxysmal pertussis-like cough from 6th to 10th month cyanosis, no whoop	None
10	1926	Gross (Case 10)	Pancreatic atrophy in infancy and childhood	Cachexia	Bronchitis	None
11	1926	Gross (Case 18)	Same	Heubner-Herter disease	Pneumonia at 19 mo.	None
12	1927	Soecknick and Thoenes	Familial pancreatic insufficiency	Fatty stools from 13 mo. until 17 mo.	No mention	1 brother of 7 years, hydrocephalus-fatty stools; 1 sister 9 mo., fatty stools died of bronchopneumonia
13	1932	Siwe	Exocrine function of pancreas and results of its cessation	Diarrhea at 6 mo.	Several bouts of bronchitis	None
14	1933-1934	Huet	Herter's infantilism and chronic lung affection	Large, thin diarrheal stools since infancy	Chronic bronchitis since 2nd year; febrile periods with cough	None
15	1935	Hess and Saphir	Celiac disease	Frequent bowel movements shortly after birth; large size stools, 4-6 daily	Admitted to hospital with diagnosis of bronchopneumonia at 9 mo.	None
16	1935	Hess and Saphir	Same	Frequent stools dating shortly from birth until 6 mo. of age	Admitted with diagnosis of influenzal pneumonia	None
17	1935	Hess and Saphir	Same	Failure to thrive from 2nd month. Attacks of diarrhea at 4 mo.	Pneumonia at 18 mo.	None

CONT'D

OUTCOME AND MANNER OF TERMINATION	POST-MORTEM FINDINGS			REMARKS
	PANCREAS	LUNGS	LIVER	
Died at 10 mo. of bronchopneumonia	Cystic degeneration of pancreas; increased interlobular connective tissue	Purulent catarrhal bronchitis; fresh lobular pneumonia	Fatty infiltration	Tuberculosis suspected; father had tuberculosis. Tuberculin negative. No tuberculosis on autopsy. Patient one of twins; other child well at 5 years
Died at 3¾ months of cachexia and bronchitis	Cystic degeneration of acini with retained secretion; dilated ducts; increase in islands of Langerhans	Pneumonia, no details	Not given	Classified by author as belonging to same group as Passini's and Burghard's cases
Died of pneumonia at 19 mo.	Almost total atrophy of secreting parenchyma; increase in number of islands of Langerhans	Pneumonia, no details	Not given	
No mention	Not given	Not given	Not given	3 members in same family with fatty diarrhea, one dying of bronchopneumonia. Author cites resemblance to Garrod and Hurtley's cases
Died of bronchiolitis at 2 years	Almost totally absent acini; islands of Langerhans well preserved	Bronchiolitis, no details	Mild, fresh cirrhosis	
Died at 10 yr. of bronchopneumonia	Marked atrophy of acini; hypertrophy of islands of Langerhans	Diffuse bronchopneumonia; bronchi and bronchioles widened and thickened walls	Fatty degeneration with secondary cirrhosis	Tuberculosis suspected during life; ruled out
Died at 9 mo. of bronchopneumonia	Much new connective tissue; acini small; ducts dilated and filled with concrements; islands of Langerhans enlarged	Bilateral bronchopneumonia with abscess formation; bronchi filled with pus	Fatty infiltration centrally located	
Died at 18 mo. of influenzal bronchopneumonia	New formation of connective tissue; normal pancreatic architecture destroyed; ducts distended with granular debris; islands of Langerhans seemed larger than usual	Bilateral bronchopneumonia, alveoli containing pus cells and many monocytes filled with fat	Fatty infiltration centrally located	Foam cells in lungs. Rickets present. Food allergy considered at 10½ mo.
Died of athrepsia at 3 yr.	New connective tissue formation; dilated ducts; large islands of Langerhans	Bilateral bronchopneumonia; pus and foam cells in alveoli	Diffuse fatty infiltration	Foam cells in lungs

TABLE I

NO.	YEAR	AUTHOR	TITLE OF REPORT (ENGLISH TRANSLATION WHERE INDICATED)	CHIEF SYMPTOMS OR SIGNS APPROXIMATE AGE OF ONSET		FAMILY INCIDENCE
				INTESTINAL	RESPIRATORY	
18	1935	Parmelee	Pathology of steatorrhea	Difficulty in feeding since birth; frequent, large, liquid, rancid stools since birth	Sinusitis and bronchitis since 11 years of age	None
19	1935	Parmelee	Same	Large loose stools from first week of life	Bronchitis during last 2 mo. of life	None
20	1936	Fanconi, Uehlinger and Knauer	Celiac syndrome with congenital cystic fibromatosis of the pancreas and bronchiolectasis	Failure to thrive; loose foul smelling stools since birth	Cough at 3½ mo.; chronic bronchitis	None
21	1936	Same	Same	Diarrhea, large, foul smelling clay-colored stools since birth	Cough since 6 mo. of age	Sibling died of similar affection (chronic bronchiolitis with dystrophy) at 14 mo.
22	1936-1937	Garsche	Clinical picture and pathogenesis of pancreatic insufficiency	Fatty stools from 18 mo.	Grippal pneumonia at 4⅓ yr.	None
23	1937	Lucksh and Sachs	Post-mortem findings in a questionable case of indigenous sprue	Profuse fatty stools since age of 22 yr.	Pneumonia at 24 yr.	None
24	1937	Campanneci	Chronic idiopathic steatorrhea associated with asthmatiform bronchietasic bronchitis	Since 33 yr. of age 7-8 frothy, viscid, glossy, mucoid stools daily	Since the age of 35, cough, mucopurulent expectoration, fever, nocturnal asthma	None
25	1938	Harper	Congenital steatorrhea due to pancreatic defect	7-14 stools daily since birth	No mention	None

CONT'D

OUTCOME AND MANNER OF TERMINATION	POST-MORTEM FINDINGS			REMARKS
	PANCREAS	LUNGS	LIVER	
Died at 14 yr. of chronic bronchitis	Fibrosis; atrophy of acini; dilatation of ducts; relative decrease in islands of Langerhans in number; increase in size	Purulent bronchitis; dilated bronchioles; fibrosis; bronchopneumonia	Chronic passive congestion	
Died at 4½ yr. of bronchopneumonia	Atrophy of acini; dilatation of ducts; relative increase of stroma; scattered islands of epithelial tissue as large as glomeruli (islands?)	Extensive subacute bronchopneumonia; miliary abscess; mucopurulent bronchitis and bronchiolitis	Marked fatty changes	Glycosuria during last 2 mo. of life
Died at 3 yr. of fever and pyelonephritis	Fibromatosis of pancreas; cyst formation of acini; large, well-preserved islands of Langerhans	Bronchiectasis with secondary purulent bronchitis; partial atelectasis	Fatty degeneration	
Died at 10 mo. of bronchopneumonia	Cystic dilatation of acini and outlet ducts; marked fibromatosis; well preserved islands of Langerhans; increased in number	Sacculated bronchiectasis of both lower lobes	Not given	Atrophy of thymus; cough resembled pertussis. Stool had 52% nitrogen and 50% fat of feedings. (See Thaysen.)
Died of grippal pneumonia at 4⅓ yr.	Connective tissue infiltration; atrophic acini; dilatation of ducts; well-preserved islands of Langerhans	Grippal pneumonia, details not given	Diffuse, fatty; large droplets, infiltration, beginning cirrhosis	
Died of bilateral lobular pneumonia at 24 yr.	Atrophic acini; normal islets	Bilateral lobular pneumonia; pleural exudate	Fatty cirrhosis	Nontropical sprue in an adult
Alive				Nontropical sprue. Respiratory symptoms antedate intestinal
Died at 3⅓ yr. of generalized tuberculosis	Pancreas a mass resembling fat; acini gone except for few near islands; latter few but normal	Not given	Fatty degeneration involving all zones least near portal area	Tuberc. probably an intercurrent infection. Adherence of pancreas suggested fat replacement or underdeveloped pancreatic tissue. 24% of stool-fat, 65% unsplit

TABLE 1

NO.	YEAR	AUTHOR	TITLE OF REPORT (ENGLISH TRANSLATION WHERE INDICATED)	CHIEF SYMPTOMS OR SIGNS APPROXIMATE AGE OF ONSET		FAMILY INCIDENCE
				INTESTINAL	RESPIRATORY	
26	1938	Harper	Same	Fatty, green stools; 5-10 daily since birth	Bronchopneumonia at 2½ mo.	None
27	1938	Harper	Same	Foul stools from birth, no weight gain	Bronchopneumonia	None
28	1938	Harper	Same	Bulky, pale, oily stools, 6 daily from birth	Subject to attacks of bronchitis	None
29	1938	Harper	Same	Pale, green or creamy yellow, rancid, bulky stools from birth	Developed bronchopneumonia during first 6 mo. of life	15 mo. old brother is passing fatty stools and is subject to frequent attacks of bronchitis
30	1938	Harper	Same	At 3 mo. large, foul smelling stools	Bronchopneumonia at 8 mo.	None
31	1938	Harper	Same	Bulky, oily stools at 3 mo.	Frequent attacks of bronchitis; pneumonia twice	None
32	1938	Harper	Same	Large, offensive, pale stools, 6 daily since the age of 5 wk.	Prolonged illness with pneumonia	None
33	1938	Rauch, Litvak, and Steiner	Congenital familial steatorrhea with fibromatosis of the pancreas and bronchiolectasis	Large, slimy diarrheal movements from birth	Wheezing since the age of 2 mo. Croupy paroxysmal cough at 6½ mo.	Brother 2½ yr. old with similar condition
34	1938	Rauch, Litvak, and Steiner	Same	4-6 stools daily, some foul smelling, some watery since 1 mo. of age	Persistent cough since birth, becoming paroxysmal at 9 mo., followed by frequent bouts	Sister, 7½ mo., died of similar condition

CONT'D

OUTCOME AND MANNER OF TERMINATION	POST-MORTEM FINDINGS			REMARKS
	PANCREAS	LUNGS	LIVER	
Died at 2½ mo. of bronchopneumonia	Pancreas small; acinar cells small, ducts distended with albuminous material; islets, small, normal	Bronchopneumonia, details not given	Patchy, fatty infiltration	Immaturity affecting acinar cells with compensatory fibrosis in stroma; 57% of dried feces was fat, 82% was unsplit
Died of bronchopneumonia at 7 mo.	Small, distended acini; ducts distorted and distended with albuminous material; islets small, normal; marked intralobular and interlobular fibrosis	Bronchopneumonia, details not given	Pale and fatty	Immaturity of pancreas with fibroid hyperplasia. 59% of stool was fat, 3% of which was unsplit
Died of bronchopneumonia at 13 mo.	Acini few, widely separated by stroma; acinar cells normal; ducts not dilated; islets conspicuously large, stroma superabundant	Pneumonia, details not given	Not mentioned	Appearance of pancreas suggests picture of immaturity. 40.8% of feces was fat, 12% of which was unsplit
Died of bronchopneumonia in second half of first year	No post-mortem	No post-mortem		Urine occasionally showed small quantities of sugar. 47% of feces was fat, 63% was unsplit
Died at 8 mo. of bronchopneumonia	No post-mortem	No post-mortem	No post-mortem	45% of feces was fat, 60% unsplit
Died at 4½ yr. of bronchopneumonia	No post-mortem	No post-mortem	No post-mortem	71% of feces was fat, 39.5% unsplit
Died at 3 years of pneumonia	Small, nodular, numerous semitransparent cysts of pinhead size; marked atrophy of acini with dilatation of ducts; islets relatively normal	No mention		44% of feces was fat, 59% unsplit
Died at 7 mo. of bronchopneumonia	Intralobular and interlobular fibrosis; acini scant; ducts distended and filled with pink-staining material; isles of Langerhans large and well preserved	Bronchitis; bronchiolitis; purulent bronchiolectasis; focal pneumonia	Fatty changes	Had pertussis-like cough; glycosuria
Died at 2½ yr. of bronchopneumonia	No post-mortem			Pertussis-like paroxysmal cough. Asthmatoid bronchitis

toms. It is our belief that there is no cause-and-effect relationship between them. We are of the opinion that their association is based on a common etiological factor, namely, a congenital anomaly of the lungs and the pancreas. Discussing first steatorrhea, Garrod and Hurtley[5] felt that their patients were the subjects of a rare inborn error of fat absorption, probably a Mendelian recessive characteristic. While their investigation did not determine for them where this error lay, it was perhaps because they did not include post-mortem studies. Passini[29] suggested, because of the rapid succession of the birth of two of his patients, that a familial congenital change in the vital organs might have been produced. Pipping[44] believed that some constitutional anomaly was the basis of the disease, pointing to the central nervous system and a constitutional inferiority in his cases. Burghard[33] and Harper[28] both suggested that the steatorrhea was due to a failure of normal development of the pancreas in utero.

In considering the defects of the lungs and pancreas as congenital anomalies, it would be well to refer to their embryologic development. Their anlages are derived from a common entodermal tube, in relatively close proximity of each other, and they begin to appear at nearly the same time. The anlage of the respiratory organs appears in the 5 mm. embryo as a groove in the floor of the entodermal tube just caudad to the pharyngeal process. The entodermal anlage of the lungs and trachea is developed in a median mass of mesenchyma dorsal and cranial to the peritoneal cavity. The terminal branches of the bronchi are lined with entodermal cells. The air cells or alveoli of the lungs begin to form in the sixth month. Elastic tissue appears during the fourth month in the largest bronchi. The abundant connective tissue found between the bronchial branches in early fetal life becomes reduced in its relative amount as the alveoli of the lungs are developed. The compact fetal lung tissue resembles that of a gland in structure becomes light and spongy owing to the increase in size of alveoli and blood vessels.

Two pancreatic anlages are developed almost simultaneously in embryos of 3 to 4 mm., a dorsal from the duodenal wall and a ventral between the hepatic diverticulum and the gut. Both form ducts. In embryos of 20 mm. the tubules of the dorsal and ventral anlages interlock. Eventually anastomosis takes place between the two ducts. In fetuses of 40 to 50 mm. the alveoli of the glands are developed from the ducts as darkly staining cellular buds. The islands also bud from the ducts and alveoli appear first in the tail at 55 mm. Kartagener and Horlacher,[48] in describing cases of familial bronchiectasis with situs inversus and polyposis, presented much evidence to support the argument for the congenital hereditary nature of bronchiectasis with malformation of the pancreas. Fanconi and his associates[38] believed that bronchiectasis with malformation of the pancreas and chronic nutritional insufficiency was both congenital and hereditary.

Scheidegger[49] felt that widening of bronchi present before birth results from a failure of development of the anlage of the respiratory organs. Heller,[50] quoted by Scheidegger, came to the conclusion that in atelectatic lung tissue the alveoli almost disappear, while the bronchi become wider as a result of the lack of back pressure from air-containing alveoli. It has been pointed out that connective tissue is abundant early in fetal life in the lungs and probably also in the pancreas. In this connection it might be stated that the reports of the pathologic findings in the pancreas in Harper's cases stressed the fact that the indications were those of an immaturity affecting primarily the acinar cells, with compensatory fibrosis most conspicuous in the alveolar stroma, and signs of degeneration. It is worthy of note, too, that Greenberg[37] in 1933, attempting to reproduce celiac disease experimentally in young animals by excluding the external secretion from the intestines, succeeded in securing a condition more nearly resembling that of congenital pancreatic insufficiency. The earliest changes two weeks after ligation of the ducts were degenerative processes in the acinar cells of the pancreas, a marked infiltration of mononuclear cells, and a slight increase in connective tissue. In later stages the amount of connective tissue steadily increased, the number of infiltrating mononuclear cells diminished, and the acinar tissue was hardly recognized as such. In the final stage of fibrosis, six to ten weeks after operation, the gland was completely replaced by connective tissue except for the islands of Langerhans which persisted throughout. All the organs appeared normal. No keratinization was noted in the trachea, bronchi, or esophagus.

It is conceivable that somewhere in the development of both pancreas and lungs, as a result of budding from their original ducts, a constriction of some of the excreting ducts (bronchial passages) may occur. The result would be a picture resembling both the experimentally produced obstruction, and post-mortem findings in reported cases. Delafield and Prudden[51] described retention cysts of the pancreas due to obstruction of the duct of Wirsung from within by a concretion or from without, which may involve the entire passage in dilatation; or the smaller tributary ducts alone may be dilated, perhaps from the presence of chronic fibrotic changes in the organs so as to form a number of small cysts. The intensity of symptoms and the duration of life would depend, among other things, upon the degree to which the structure of the organ was anomalous, and on the number and kinds of infection to which the patient was exposed. That an anomalous organ is highly susceptible to noxious influences is well known.

The presence of repeated bronchitis, purulent bronchiolitis, abscess formation, and empyema could thus be accounted for without invoking the theory of direct damage by irritating substances, the products of abnormal digestion, carried to the lungs by way of the blood stream. This suggestion has been made by Parmelee,[24] and earlier by Herter,[4]

Poynton and his group,[6] and Still[8] to account for the complications of the celiac disease. Against Parmelee's other suggestion,[24] namely, the deprivation of a fat-soluble vitamin owing to defective absorption of fats, resulting in lowered resistance to infection, is the absence of any visible evidence of hypovitaminosis A clinically and pathologically. While the deficiency of vitamin A has been reported (Schick and Wagner[30]), this has been the exception.* The presence of cough from birth in our Case 2 and its appearance shortly after birth in Case 1 lend further support to the theory of the independence of the respiratory symptoms from the digestive disturbance.

Several other minor points are worthy of mention. The familial incidence of the steatorrhea occurred also in cases reported by Poynton and his collaborators,[6] Fanconi and his associates,[38] Pipping,[44] Passini,[29] Soecknick and Thoenes,[23] Garrod and Hurtley,[5] and Harper.[28] While Haas[52] has referred to a similar incidence in celiac disease, it would be interesting to reanalyze his series to determine if any of his cases could be classified with the pancreatogenous steatorrheas.

The suspicion of tuberculosis to account for the clinical picture in our cases was also entertained by both Huet[36] and Burghard,[33] and presumably excluded ante mortem by negative intradermal tuberculin tests, and post mortem by the absence of the specific pathology of this disease.

Another very remarkable phenomenon was the striking resemblance of the cough in both children to that of pertussis. There were paroxysms, suffusion of the face and eyes, and cyanosis, but rarely vomiting and never the characteristic whoop. Nor did the laboratory evidence support this diagnosis. The patients of Burghard[33] and Fanconi and coworkers[38] had similar coughs, as well may have had those patients classed as "influenzal" or "grippal" pneumonia described by Moorhead,[53] Garsche,[39] and Hess and Saphir.[14]

The transitory presence of glycosuria in our first case is a rare, but not undescribed, occurrence. This was present in the patient of Garrod and Hurtley,[5] although they laid no great stress upon it. Bramwell[20] quotes a case of Moorhead's[53] that exhibited this feature. A similar experience was noted by Parmelee in one of his patients and by Harper[28] in one of hers. While Burghard[33] remarked that he had not found it in his own case, he quotes Körte as having observed it in 8 out of 119 cases of disturbances of the pancreas, excluding diabetes mellitus. Poynton and Cole[56] in 1925 reported a patient 6 years 9 months old as a case of celiac disease with glycosuria. Although the ordinary tests showed no evidence of pancreatic insufficiency, the facts that in the beginning the urine became sugar free with dietary regulation alone in so young a child and that the celiac syndrome had its onset at three months suggest that they may have been dealing with a pancreatog-

*Since the completion of this paper, Dr. Dorothy Andersen has referred to several other cases showing vitamin A deficiency (Am. J. Dis. Child. August, 1938).

enous steatorrhea. The authors proposed the possibility that chronic irritation of fatty stools with a high percentage of fatty acids brought about an attack of an acute gastroenteritis during which poisons absorbed from the intestines acted on the islets of Langerhans. Thaysen[25] has emphasized that in many cases of pancreatogenous steatorrhea the sugar tolerance curve may approach the diabetic type. Encroachment of fibrous tissue on the island of Langerhans might explain this phenomenon together with the glycosuria, but could not account entirely for the rarity and transitory nature of the latter.

The significance of the fatty changes in the liver present in our Case 1 together with similar changes, and in some instances early cirrhosis reported in the cases of Poynton, Armstrong and Nabarro,[6] Clarke and Hadfield,[31] Pipping,[44] Mautner,[32] Burghard,[33] Siwe,[35] Huet,[36] Hess and Saphir,[14] Parmelee,[24] Fanconi, Uehlinger and Knauer,[38] Luckseh and Sachs,[40] and Harper,[28] is not clear. Still[8] found the liver to be normal on section in cases of celiac disease. Whether fatty liver with cirrhosis should be considered as a process secondary to the pancreatic insufficiency or like the pulmonary and pancreatic abnormalities, an independent phenomenon and part of the syndrome, is difficult to decide.

SUMMARY

Two cases of congenital familial steatorrhea with fibromatosis of the pancreas and bronchiolectasis are presented, one with post-mortem findings.

The past and present concepts of the terms "steatorrhea" and the "celiac syndrome" are described.

The steatorrheas are classified as the idiopathic variety, including celiac disease, and the pancreatogenous. Into the latter division fall most of the cases reported in the literature, which begin soon after birth, are refractory to treatment, and show characteristic post-mortem changes in the pancreas. This includes one and presumably the other of our cases.

Suggestions for the recognition of these cases are offered.

The association of respiratory symptoms and pulmonary findings with the steatorrheas is discussed, and the reasons for considering the pathologic phenomena of both pancreas and bronchi to be based on congenital anomalies are given.

The appearance of symptoms from birth, the familial incidence of the disease, the characteristic pertussis-like cough, the presence of transitory glycosuria, and the finding of fatty changes in the liver are mentioned.

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NOTE.—Since this paper was completed the article of Dr. Dorothy H. Andersen, "Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease," and that of Dr. John Thomas and Dr. F. M. Schultz, "Pancreatic Steatorrhea," appeared in the August, 1938, issue of the *American Journal of Diseases of Children*.

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TREATMENT OF RICKETS AND TETANY WITH A SINGLE MASSIVE DOSE OF VITAMIN D

Vitamin D Shock Therapy

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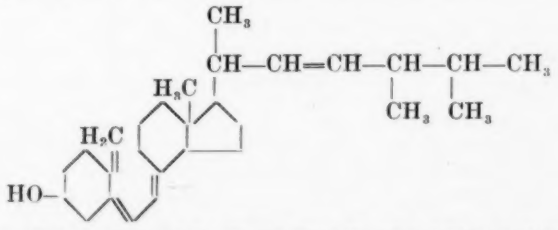
IN 1928 I[1] reported that it is possible to prevent and cure rickets in rats with one single subcutaneous or peroral dose of 1 mg. of irradiated ergosterol, i.e., more than a thousand times the effective single daily dose. These experiments showed that the rachitic rat is capable of retaining from a single massive dose as much vitamin D as is necessary for the prevention and cure of rickets.

In addition, six rachitic infants were treated with total amounts of 70 to 120 mg. of irradiated ergosterol, divided into several doses and administered subcutaneously as well as orally. In order to avoid untoward effects, only fourteen to twenty-four times the effective daily dose was used, as compared with the thousand fold single dose which was administered to rats. Nevertheless, the rickets was cured by this therapy, although the speed of healing was not impressive or even satisfactory. Since in 1928 and the following years the available vitamin D preparations contained toxic by-products, for instance toxisterol, it was not justifiable to continue these experiments or to increase the doses.

In 1929 Petényi[2] repeated my clinical experiments in several rachitic children and observed that the healing process began after three days and was completed within seventeen days. Subsequently Göttche,[3, 4] in 1930, treated eleven children, nine of them with 100 mg. of devitol (calculated by him to contain about 750,000 international units vitamin D) and two with 50 mg. of devitol. The smaller doses proved to be insufficient. Of the nine children treated with the larger doses, however, five were completely cured, and four showed a delayed or unsatisfactory response to this "shock therapy" *(Stosstherapie)*.

Several years later, particularly through the studies of Windaus and Holtz, a further purification of vitamin D was achieved. The elimination of toxisterol from the irradiated ergosterol resulted in a purer, more effective, and nontoxic preparation which was first named vitamin D_x, and subsequently vitamin D_2. The formula is as follows:



From the pediatric service of the Mount Sinai Hospital (chief of staff, Dr. Béla Schick), New York.

With this pure, nontoxic product, any objection to further investigation of the single dose treatment was removed.

Since 1936 Harnapp,[5] Schirmer,[6] Bischoff,[7] Braulke,[8] Windorfer[9] and I resumed this clinical investigation. More than 150 rachitic and tetanic children were successfully treated. Table I summarizes the reports in the literature.

TABLE I

AUTHOR AND YEAR	NUMBER OF CASES	PREPARATION	TOTAL DOSE	INT. UNITS	DAMAGE	RESULTS
Vollmer[1] 1927, 1928	6	vigantol	70-120 mg.	100,000-180,000	none	Slow healing.
Petényi[2] 1929	"several"	vigantol	100 mg.	150,000	none	Good.
Göttche[3] 1930	9 2	devitol devitol	100 mg. 50 mg.	750,000†* (150,000) 375,000†* (75,000)	none none	Prompt or delayed, unsatisfactory.
Harnapp[5] 1936	15	vitamin D_3	12-15 mg.	600,000-750,000 (480,000-600,000)	none	Accelerated healing in rickets and tetany.
Schirmer[6] 1936	30	vitamin D_X	0.2-0.5 c.c.	240,000-600,000	none	Prompt or insufficient.
Bischoff[7] 1937	10	vitamin D_2	15 mg.	600,000	none	Prompt, no recurrence.
Braulke[8] 1937	50	vitamin D_2	15 mg.	600,000	none	Accelerated healing, not disturbed by infections.
Windorfer[9] 1938	21	vitamin D_2	6-15 mg.	240,000-600,000	none	Good.
Harnapp[5] 1938	11	vitamin D_3†	7.5-15 mg.	300,000-600,000	none	Good only with 10 and 15 mg.
Vollmer 1938	6	"Ertron"	12 capsules	600,000	none	Prompt, good results.

*This calculation seems to be erroneous. The result of my calculation is 100 mg. devitol = 150000 units; 50 mg. = 75,000 units.

†Vitamin D_3 is produced by irradiation of 7-dehydrocholesterol which represents the provitamin of D_3. Vitamin D_3 is found in cod-liver oil, not in irradiated ergosterol.

In the second half of the winter 1937-1938, I treated six cases of rickets and tetany with a single massive dose of vitamin D. The preparation "ertron" from the Nutrition Research Laboratories, Chicago, was used.* This contains 50,000 international units vitamin D per capsule. Since the 600,000 units which were usually administered make considerable bulk, the powder was divided into two parts and emulsified in two consecutive bottles of milk, usually administered on the same day. As examples, three clinical reports with x-ray and laboratory data are given.

CASE 1.—A six-month-old colored boy who was well until a week before admission Jan. 25, 1938, developed a cold and running nose. For three days before admission the child had a dry cough and slight fever. The patient had been fed

*Pure crystalline vitamin D_2 in concentrated solution is preferable. It was used with the same favorable results in 7 additional cases of rickets and tetany in the winter of 1938-1939.

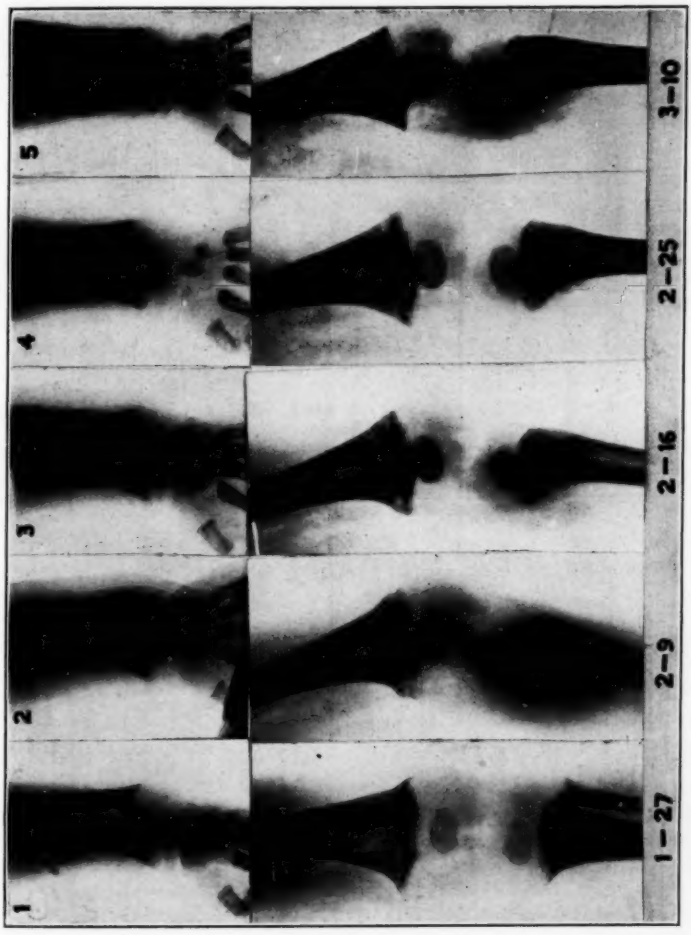


Fig. 1.—Case 1. Roentgenograms of patient treated with 600,000 units of vitamin D, January 28. *1*, (1/27/38) Active rickets, before treatment. *2*, (2/9/38) Healing in progress, 12 days after treatment, showing new line of calcification in metaphyses. *3* and *4*, (2/16/38 and 2/25/38) Healing, 19 and 28 days after treatment; gradually increasing density of lines of calcification. *5*, (3/10/38) Complete healing, 41 days after treatment.

on nonirradiated evaporated milk, had never received breast milk, but had received 2 teaspoonfuls of orange juice daily for two months before admission, and 1-2 teaspoonfuls of cod-liver oil daily for one month before admission. The child had had very little exposure to sunlight, and there were no other sources of vitamin D.

Physical examination showed a malnourished child, breathing rapidly and shallowly. The anterior fontanel was wide open; the posterior portion of the sagittal suture and a small portion of the posterior fontanel were still open. Definite craniotabes, prominent rachitic rosary with slight depression of the sternal plate, and slight flaring of the costal margin were present. The legs bowed anteriorly to a slight degree. There were wheezes and râles in the lungs; the pharynx was reddened. The urine was negative, the Schick test, positive. Mantoux, Pirquet, tuberculin patch test and the Wassermann test were all negative. Hemoglobin was 78 per cent, red cell count 3,800,000, and white cell count 12,000 with 80 per cent polymorphonuclears.

Serum phosphorus was 3.5 mg. per cent; calcium, 7.7 mg. per cent. X-ray (Fig. 1) showed general decalcification of the bones with cupping and irregularity of the metaphyses and slight periosteal changes.

The therapy used was 600,000 internationnl units of vitamin D, in two doses, administered January 27 and 28.

TABLE II

COURSE

DATE	CLINICAL SYMPTOMS	X-RAY (FIG. 1)	SERUM	
			CA	P
1/27/38	Severe rickets	Active rickets	7.7	3.5
1/27 and 28/38	600,000 units vitamin D (ertron) by mouth			
2/ 1/38	Happy, active		10.5	5.2
2/ 9/38	Good condition	Marked calcification		
2/14/38	Good condition		11.0	5.2
2/16/38	No craniotabes	Zone of provisional calcification well calcified		
2/25/38			10.9	7.2
3/10/38	Good condition		10.4	6.0

Summary.—A case of severe active rickets in a 6-month-old colored boy was treated with 600,000 units of vitamin D in two doses. Within four days (or earlier) the low phosphorus and calcium levels rose to normal values. After twelve days (or earlier) distinct roentgenographic evidence of healing rickets was present, several roentgenograms (Fig. 1) showed continuous improvement and complete healing within 41 days. Since the second day after the treatment, the boy was happy and active, took his feedings well, gained weight. The craniotabes disappeared within 19 days.

CASE 2.—A 12-day-old male infant, born normally. Began, two days before admission, to have very frequent generalized twitching of the facial muscles, the arms and the legs, associated with regurgitation of a small amount of the previous feed-

TABLE III

COURSE

DATE	CLINICAL SYMPTOMS	SERUM	
		CA	P
3/11/38	General convulsion; Chvostek +++. 5 c.c. of 10% calcium gluconate	6.0	--
3/12/38 A.M.	Convulsion, Chvostek +++.		
3/12/38 P.M.	600,000 units vitamin D by mouth		
3/13/38	No convulsion or twitching		
3/14/38	Quiet, sleeps and drinks well Chvostek, peroneal, Trousseau, all negative	--	6.5
3/15/38	Good condition	11.2	7.1
3/18/38	Good condition	10.6 Phosphatase: 4 King-Armstrong units	--

ing. There was no evidence of any dietary inadequacy in either the mother or the child. The child was admitted to the hospital March 11, 1938.

Physical examination showed a normally developed infant. There were frequent convulsive seizures lasting about 3 minutes, particularly when the infant was disturbed. These consisted of generalized twitching of all extremities, the mouth and eyelids. There was no definite carpopedal spasm. An inconstant Chvostek sign and a negative Trousseau sign were noted. The urine was negative; the hemoglobin, 125 per cent; the blood sugar, 70 mg. per cent; and the serum calcium, 6.0 mg. per cent. X-ray films of the long bones showed increased density and lack of definition of the trabecular structure in the metaphyseal ends.

The therapy instituted was 5 c.c. of 10 per cent calcium gluconate intramuscularly, March 11; 600,000 units vitamin D by mouth, March 12, at 6 and 10 P.M.

Summary.—Neonatal low calcium tetany was found in a 12-day-old infant. The generalized twitching was not controlled by calcium gluconate and recurred the following day, before 600,000 units vitamin D were given by mouth. After this therapy the twitching did not reappear. Within two days the Chvostek sign had disappeared; within three days the serum calcium had risen from 6.0 to 11.2, with the serum phosphorus as high as 7.1 mg. per cent. The infant was comfortable, slept and took his feeding well, and was discharged at the end of nine days. No additional calcium or acid therapy was given, except on the day of admission.

CASE 3.—A 5-month-old infant had a history which was entirely negative; she was born normally and was breast fed for three months. For two months before admission she had been receiving evaporated milk, no orange juice, and no cod-liver oil. One week before admission she developed an upper respiratory infection. The night before admission she became irritable and fretful, and on the morning of admission she had a generalized convulsion, opisthotonus with extension of the arms and legs. The child was admitted to the hospital Feb. 19, 1938.

Physical examination showed a child with marked craniotabes and slight beading of the costochondral junctions. The Chvostek reflex was equivocal, and the Trousseau sign, negative. There was some reddening of the pharynx. The urine showed one-plus albumin, and 15 white blood cells per low powered field. Wassermann, Schick, Mantoux, Pirquet tests and tuberculin patch test were all negative. Hemoglobin was 78 per cent; red blood cells, 4,920,000; white blood cells 6,800 with 58 per cent polymorphonuclears. The serum calcium was 6.5 mg. per cent;

TABLE IV

COURSE

DATE	CLINICAL SYMPTOMS	SERUM	
		CA	P
2/19/38 A.M.	Generalized convulsion	6.5	5.5
2/19/38 P.M.	600,000 units vitamin D by mouth		
2/21/38	Chvostek, negative	7.5	5.7
2/23/38	Good condition	8.6	--
3/ 5/38	No craniotabes	10.0	6.9

the serum phosphorus, 5.5 mg. per cent. X-ray films of the skull, long bones, and chest did not show any abnormalities.

The therapy employed was 600,000 units vitamin D by mouth, February 19.

Summary.—This was a case of low calcium tetany with generalized convulsions in a child with rickets. Tetany was precipitated by an upper respiratory infection. On the day of admission the child received 600,000 units vitamin D by mouth. Thirty-six hours after admission the calcium had risen from 6.5 to 7.5 mg. per cent; Chvostek sign was definitely negative; after the vitamin D therapy no recurrence of convulsions was observed. The serum calcium rose gradually up to 10.0 mg. per cent on the fourteenth day. The phosphorus remained on normal level, increasing from 5.5 to 6.9 mg. per cent. The craniotabes disappeared within sixteen days. The child was in good condition.

DISCUSSION

1. *Curative Effect.*—(a) In Rickets: A single dose of 600,000 international units of vitamin D cures rickets in a relatively short time. Very early, one to three days after the administration, a change takes place in the general condition and the mood of the child. He becomes happy and active—an observation which is also stressed by Schirmer,[6] Bischoff,[7] Braulke,[8] and Windorfer.[9] The craniotabes disappears within two to three weeks, although improvement may be observed as early as the first week.

In cases in which the serum phosphorus level was determined early, it was found normal within four days. In all the other cases it was normal when the first determination was made—six to nine days later. The values sometimes exceeded 7 mg. per cent. Accordingly, the vitamin D shock therapy seems to increase the serum phosphorus in a shorter time than the usual treatment with daily small doses. Hypernormal values of serum phosphorus usually decline in two to four weeks after the treatment, but remain high normal or normal for several weeks. The speed in the rise of phosphorus seems to depend on the vitamin D dosage. Serum calcium, when low, reaches or exceeds normal values within two to four days.

The roentgenographic evidence of calcification in the long bones appears earlier than with the usual method of vitamin D therapy or with ultraviolet irradiations. Our x-rays usually were taken too late to discover the very first appearance of recalcification, the speed of which exceeded our expectation. In Case 1 the second roentgenogram, taken twelve days after the treatment, already showed advanced ossification. Forty-two days after the vitamin D shock therapy, this child showed roentgenographic evidence of complete restitution of the rachitic defects of the long bones, the former rachitic process being indicated merely by the transverse line (Fig. 1). In a case of scurvy with rickets com-

bined vitamin C and D therapy brought about distinct ossification of the subperiosteal hemorrhage within five days. Calcification proceeded rapidly, became very dense, and was completed after about four weeks. Petényi,[2] Schirmer,[6] Braulke,[8] and Harnapp,[5] observed accelerated roentgenographic ossification with the vitamin D shock therapy as compared with the previous method. Harnapp and Braulke followed some of their patients over a period of five months and did not observe any recurrence of the rachitic process.

(b) In Infantile Tetany: The effect of the single dose treatment of infantile tetany is striking. Without any additional therapy—for instance acid, ammonium chloride, calcium, or sedatives—general convulsions do not reappear after the administration of 600,000 units of vitamin D. The signs of mechanical hyperirritability disappear within two days. In Braulke's experience,[8] it took as long as five days in only a few cases. The rapid rise of the serum calcium is the most impressive effect. In Case 2 (neonatal tetany) there was a rise from 6.0 to 11.2 mg. per cent within sixty hours, all clinical symptoms subsiding during the first day. All other authors agree in stressing this immediate increase of serum calcium to normal or hypercalcemic values up to 13.5 mg. per cent. Our figures, however, did not exceed 11.2 mg. per cent, the difference probably depending upon the purity of the vitamin D preparation. Undoubtedly, no other therapy has such an immediate and lasting effect as the treatment with a single massive dose of vitamin D.

2. *Indications.*—The question arises whether this vitamin D shock therapy is definitely superior to the previous method and, if so, in what type of case. Göttche[3] and also Windorfer[9] question its superiority in the treatment of uncomplicated rickets. Other authors were not satisfied with the results in several such cases—an opinion which I shared ten years ago. I have since realized that it is a matter of dosage. This will be discussed later.

Surveying all reports in the literature and my own recent experience, I conclude that the following are definite indications for vitamin D shock therapy:

1. neonatal and infantile tetany
2. severe rickets
3. pneumonia or pertussis associated with active rickets
4. chronic infections associated with rickets—since every chronic infection seems to impair materially the utilization of vitamin D
5. indifference or unreliability of the parents of a rachitic or tetanic child.

3. *Contraindications and Toxicity.*—No contraindication seems to exist. Vomiting and diarrhea may interfere with the precision of dosage.

When the vomiting occurs, an indeterminable portion of the drug may be lost; if diarrhea occurs, the absorption of vitamin D is impaired to an uncertain extent; but both these conditions are considered also to be contraindications for the treatment with daily vitamin doses—the drug usually being discontinued until the disturbance subsides.

No evidence of toxicity or damage has been observed in our cases, and none by the other authors. The vitamin D shock therapy seems to be entirely harmless. Nonrachitic adults with arthritis have taken daily doses of 200,000 to 1,000,000 and even more units over a period of weeks, months, and years, and only very few of these have at some time manifested evidence of toxicity. The symptoms observed in these patients were nausea, increased frequency of urination (pollakiuria), lassitude, anorexia, polydipsia, diarrhea, griping pain in the gastrointestinal tract, and vomiting. These manifestations disappear as soon as the drug is discontinued, without resulting in permanent cellular injury (Dreyer and Reed[10]; Wyatt, Hicks, and Thompson[11]; Livingston,[12]; Farley[13]; Steck[14]). This should be known and borne in mind despite the fact that no toxic symptoms ever occurred among 150 or more infants and children treated with one single massive dose of vitamin to date. Moreover, toxic effects are due rather to toxic by-products (particularly toxisterol and dihydrotachysterol) than to the vitamin itself and will gradually be eliminated with the purification of vitamin D preparations. The therapeutic index of pure crystalline vitamin D_2 is as much as 1:3,500; i.e., only the 3,500 fold effective single dose may cause toxic symptoms. The dosage used, however, is far below this amount.

Electrocardiographic examinations, carried out by Schirmer[6] and Opitz,[15] did not reveal any pathology following vitamin D administration. On the contrary, the typical electrocardiographic changes in tetany, as described by Schiff, Doxiades and Vollmer[16] and Aschenbrenner and Bamberger,[17] disappear after vitamin D shock therapy with the cure of the underlying disease.

4. *Dosage and Form of Application.*—In 1927 and 1928, when my first experiments were carried out, the vitamin D preparations were not yet standardized. Subsequently, methods of standardization were repeatedly changed, thus confusing all quantitative considerations. In Table I, I tried to calculate by conversion the value of the various preparations in international units.

It is evident that the results of the single dose treatment depend, first of all, upon the dose. Doses below 200,000 units do not produce a certain and prompt effect; 200,000-400,000 units may be sufficient in younger infants and in cases of mild rickets and tetany, provided that no complication impairs the utilization of the vitamin. Doses of 600,000 international units of vitamin D resulted, without any exception, in an un-

usually prompt cure of even severe rickets and tetany, unimpaired by the presence of acute or chronic infection.

The question arises whether 600,000 units is the optimum dose for every condition and every age. The most dramatic success was obtained in a 12-day-old infant (Case 2) for whom according to body weight, half the dose necessary for a 5- or 6-month-old baby should be sufficient. This makes me believe that the optimum is above 600,000 units for infants older than 3 months old and that still better results may be achieved with higher doses.

These doses are given by mouth, the most simple and effective way of administration. Since vitamin D is better utilized when incorporated in milk (Hess[18] and J. M. Lewis[19]), the single dose should be so administered. Care should be used that no active substance is lost by adhesion to the bottle or other receptacle.

In my first publication it was proved that rickets in rats can be prevented and cured not only by oral but also by subcutaneous and intraperitoneal administration of irradiated ergosterol in oil. Previously, Hess and his co-workers,[20] and B. Kramer and his associates[21] came to the same conclusion. I have also treated three rachitic children with subcutaneous injection of 70-80 mg. of irradiated ergosterol. All of them were cured, but the healing process was delayed, obviously more because of the insufficient dose than the parenteral administration.

Undoubtedly, vitamin D is effective also when given subcutaneously or intramuscularly. The subcutaneous vitamin D shock therapy may be useful in certain cases or for certain purposes. For the general use, however, the peroral method is preferable.

5. *Prophylactic Effect.*—The prophylactic efficacy of a single dose of vitamin D in rats has been proved by the author[1] in 1927-1928. Peroral as well as subcutaneous or intraperitoneal administration of a single dose of 1 mg. irradiated ergosterol, i.e., the thousand fold effective daily dose, prevented the development of rickets in all cases in rats kept on a rachitogenic diet.

Recently, Harnapp[5] reported studies in prophylaxis in 41 infants and premature infants with single peroral doses of 5, 10 or 15 mg. of vitamin D_2 or D_3, respectively. His results are very encouraging.

This may assume significance for the future of mass prophylaxis. The preventive measures hitherto available are satisfactory from the theoretical, but by no means from the practical, point of view. Severe rickets may be almost entirely eliminated, but mild degrees occur rather frequently despite the general preventive endeavors.[22, 23] This is due partly to the indifference of some parents, partly to an aversion to medicines or to the inconvenience of the continuous medication.

If the entire prophylactic campaign could be concentrated in one single action, the results might be better. For this purpose the sub-

cutaneous administration of the vitamin dose might be superior to the peroral method, for the injection would be given by the physician himself and thus would guarantee the administration of a precise quantity at a known time.

Harnapp[5] believes from 280,000 to 400,000 units of vitamin to be the proper preventive dose. It seems to me it should be as high as the curative dose in order to achieve reliable protection. Further experience must decide the most favorable time for the vitamin D shock prophylaxis. Presumably, it will be the end of November or the beginning of December when the vitamin D reserve, stored during summer and early autumn, is about to be exhausted. This should be repeated in the second winter of life.

The possibility of a vitamin D shock prophylaxis is materially supported by the evidence that vitamin D administered in one massive dose is retained in the child system. Most of it is stored in the skin, liver, and brain, as is shown in a separate communication.[24]

SUMMARY

Rickets and tetany can be cured by peroral administration of one single dose of 600,000 international units of vitamin D.

The curative effect of this treatment is more prompt than that obtained with the daily administration of small doses.

Serum calcium and serum phosphorus become normal and roentgenographic evidence of calcification shows within one week. The most impressive effect is the rapid rise of serum calcium.

Tetanic convulsions did not recur after vitamin D shock therapy, and all other symptoms of hyperirritability disappeared usually within two days without any additional therapy.

Hypernormal values of serum phophorus may occur after vitamin D shock therapy. They usually decline to a normal level in from two to four weeks after the treatment.

The following conditions may be considered as indications for vitamin D shock therapy: neonatal and infantile tetany, severe rickets, rickets associated with pneumonia or pertussis, rickets associated with chronic infections, and indifference of the parents of a rachitic or tetanic child.

No contraindication seems to exist.

No toxicity was manifested in 150 children treated with massive doses of vitamin D.

The proper dosage is 600,000 international units, incorporated in milk.

Vitamin D is effective also when administered subcutaneously.

The possibility of a successful vitamin D shock prophylaxis over the entire winter period with a single dose of 400,000 to 600,000 units is discussed.

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25 Central Park West

TREATMENT OF EARLY MEASLES WITH PARENTAL WHOLE BLOOD

Effect on Clinical Course and Pulmonary Complications in Young Children

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PATHOGENIC bacteria are found in a number of virus diseases soon after the onset of active clinical symptoms. These bacteria are presumably secondary invaders and are thought to be the cause of the complications which often occur during the course of the primary disease, for example, the presence of hemolytic streptococci or influenza bacilli in the respiratory tract during measles.

In infants and young children involvement of the lungs in measles is frequent and serious. Post-mortem cultures of such lungs usually yield hemolytic streptococci. Less frequently pneumococci or influenza bacilli are found. In an attempt to prevent the occurrence of pneumonia in young children with measles, Chevalley, Duchon and Fourestier[1] injected one dose of 20 c.c. of diphtheria antitoxin and also 1 c.c. of a polyvalent catarrhal vaccine daily up to eight days after the onset of the illness. The mortality in the treated group was 5.1 per cent compared with 15.5 per cent in the untreated group.

It is a well-established fact that, when susceptible individuals are exposed to measles, the disease can be modified or prevented by the injection of convalescent measles serum, if given in proper dosage and within a certain time interval after exposure. Whole blood or serum in proper amounts, taken from persons who had measles some time previously, has also proved effective. The protective power of such adult blood or serum is generally regarded to be about one-third to one-fourth that of recent convalescent serum.

Modified measles runs a comparatively mild course. When compared with unmodified measles, the incidence of pulmonary and other complications is much less frequent. It was suggested, therefore, that the injection of measles convalescent serum or its equivalent in adult blood, given early in measles, might decrease the occurrence of the complications caused by pathogenic bacteria. It is possible that such sera, in addition to possessing protective substances against the measles virus, also contained antibodies against the secondary invaders. In the dose of adult whole blood proposed for injection, we did not hope for any modification of the measles itself. In another study, collaborating with others, one of us[2] found that 40 c.c. to 50 c.c. of

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TABLE I

COMPARISON OF CLINICAL COURSE AND PULMONARY COMPLICATION BY AGE GROUPS WITH AND WITHOUT USE OF BLOOD INJECTION

	AGE (YR.)	TOTAL PATIENTS	CLINICAL COURSE OF MEASLES									
			MILD		MODERATE		SEVERE		PULMONARY INVOLVEMENT		DEATHS	
			TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%
Blood injection	½-1	23	19	83.0	0	0	4	17.0	3	13.0	0	0
No injection		94	55	58.5	13	13.8	26	27.7	20	21.2	5	5.3
Blood injection	1-2	30	23	77.0	3	10.0	4	13.0	5	16.6	0	0
No injection		323	215	66.7	40	12.3	68	21.0	65	20.0	6	1.9
Blood injection	2-3	13	10	77.0	3	23.0	0	0	1	7.7	0	0
No injection		341	259	75.8	39	11.6	43	12.6	38	11.0	5	1.4
Blood injection	Totals	66	52	78.8	6	9.1	8	12.1	9	15.1	0	0
No injection		758	529	70.0	92	12.1	137	17.9	123	16.2	16	2.1

measles convalescent serum must be given intravenously in the pre-eruptive or early eruptive stages in order to modify the disease.

The work reported in this paper was done before the establishment of the Manhattan Convalescent Serum Laboratory. Large amounts of convalescent serum were not as yet available. These young children, therefore, were given whole blood injections from adults with a history of measles.

METHOD AND MATERIAL

During the winter and spring of the years 1935 and 1936, sixty-six children under 3 years of age, admitted to the Willard Parker Hospital in the pre-eruptive or early eruptive stage, were injected subcutaneously with 20 c.c. to 40 c.c. of blood taken from parents who had a history of measles. If more blood is given subcutaneously to young children, local or general reactions may occur. The course of the disease after injection was noted and classified as mild, moderately severe, or severe. By mild was meant measles that ran a benign course without complications. The children designated as moderately ill were quite toxic and had high fevers and, when complications were present, they were not very extensive or virulent. The severe cases were in those who were very ill, toxic, and who usually had extensive pulmonary involvement.

A patient was considered to have pneumonia only when there were definite clinical signs of pulmonary involvement.

RESULTS

Sixty-six children were given blood injections. Fifty-two were considered as having had a mild measles. Six children were considered to be moderately ill and eight, severely ill. In the latter two groups, nine had clinical evidence of pneumonia.

During this same period, 758 additional children, under three years of age, were admitted to the Willard Parker Hospital with measles. Since none of these children were injected with blood, their clinical course could be compared with those receiving the blood injections.

In measles, the younger the child the more frequent and the more serious are the complications. Therefore, the highest mortality occurs in the youngest age groups. The clinical course of pulmonary complications and mortality are considered according to age groups (Table I). Analyzing the data, it would appear that the clinical course of those receiving whole blood, especially in the youngest group, was a little less severe. But, since there were over eleven times as many children that did not receive blood, this difference does not have statistical significance.

COMMENTS

The subcutaneous injection of whole blood from adults with a previous history of measles seems to be of little value in reducing pulmonary complications, even if given early in the disease. It is possible that a larger amount of blood might be effective, but, as noted, this may cause unfavorable reactions. Presumably the pulmonary complications are caused by pathogenic bacteria, the so-called secondary invaders.

But, are we correct in assuming that the virus is the sole and primary etiological agent, and the bacteria encountered are merely concomitant and of secondary importance? From the work of Shope,[3] in the influenza of swine and man, consideration must be given to the fact that the bacteria may be a definite and indispensable part of an etiological complex and the bacteria must not be relegated to a secondary role. The pathologic picture of peribronchial infiltration of pulmonary involvement in measles is that often seen in diseases caused by filtrable viruses.

Serum from immune persons, therefore, may have a neutralizing effect on the concomitant bacteria as well as on the virus. With this possibility in mind we hope, some time in the future, to report on the treatment of severe pneumonia occurring mainly in the late eruptive and posteruptive stage of measles. Measles patients with severe pulmonary involvement were injected intravenously with either measles convalescent serum or scarlet fever serum. From one to three large doses were given. Thus far the results have been of questionable value.

SUMMARY

The etiological agent of measles is presumably a filtrable virus. The subsequent complications are presumably due to the presence of pathogenic bacteria. In an attempt to reduce the incidence of pulmonary complications and thus lower the mortality in children, sixty-six children under three years of age were injected subcutaneously with from 20 c.c. to 40 c.c. of adult blood during the pre-eruptive or early eruptive stages of measles.

There was very little difference in the severity of the measles or in the incidence of pulmonary involvement, when these sixty-six children were compared with 758 children in the same age group who did not receive blood injections.

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THE WATERHOUSE-FRIDERICHSEN SYNDROME

Report of a Case With Autopsy Findings

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MARCHAND[1] first described a case of Werlhof's disease which was associated with hemorrhage in both adrenal glands in a 9-month-old child, and several examples have since appeared in the literature. It was not until 1901 when Little[2] recognized as a disease entity the condition which was first described by the English physician Waterhouse,[3] and later by Friderichsen,[4] which has since been known as the Waterhouse-Friderichsen syndrome. Several examples of this condition subsequently appeared in the European literature, and in 1933 Glanzmann[5] reported a case with a review of the literature up to that time. In 1936 Aegerter[6] reported one case and included the comprehensive literature; in 1938 Usher[7] and Biddau[7a] reported similar cases.

In the aforementioned examples, as well as those who have reported cases in the European and English literature, the authors have had experiences in some of their cases in making clinical observation on their patients before death. In the case I shall present, I did not have an opportunity to examine the child before death because death was sudden and unexpected. The history as given by the mother is as follows:

V. B. L., an 18-month-old white female, who was 32 cm. in length and weighed 33 pounds, was apparently well, until one day the mother noticed the child was listless and did not respond as much as she did before. A doctor was summoned who examined the child and told the mother that the child was suffering probably from a "food poisoning." The mother then noticed a rash on the child's face and body and summoned the doctor again who thought the child had an acute infectious disease. The child died about thirty-six hours after the symptoms were noticed by the mother.

At autopsy, the entire body from the hair line on the forehead to the ankles of both feet anteriorly and posteriorly, was covered by pink to red blotches grossly resembling purpuric spots (Fig. 1). The essential pathologic findings were as follows: Thymus weighed 35 gm. but showed no gross pathologic changes. Lungs, trachea and tracheobronchial lymph glands were essentially unchanged. The heart weighed 87 gm., and except for the pale red color of the myocardium, the musculature of the heart, the valves and aorta were negative. The peritoneum was smooth and the spleen presented a follicular hyperplasia. The liver and kidneys were grossly unchanged. The pancreas, uterus, and adnexa were uninvolved, and the mesenteric lymph glands were hyperplastic. The stomach and small and large bowel showed no gross changes. The examination of the brain was grossly negative. The essential pathology was found in both adrenal glands, and these weighed 12 gm. (Fig. 1). They were red, and on section of the adrenal gland the entire surface of the cortex and medulla was markedly hemorrhagic. The hemorrhage did not involve the surrounding tissue of the adrenal gland. The heart's blood and spleen gave sterile cultures.

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MICROSCOPIC EXAMINATION

Adrenal Glands.—Sections of the right and left adrenal gland showed extensive hemorrhage in the cortex and medulla. The hemorrhage did not extend beyond the limits of the cortex. The cell outlines were indistinct, and the nuclei were irregularly distributed throughout the section and no relationship with the cell outline. Sections of the adrenal gland fixed in formalin, Zenker's solution, and alcohol showed microscopically similar changes. In some of the sections of the adrenal gland there were outlines of fat cells in the medullary portion, and the outlines of the red cells were indistinct. One portion of the adrenal gland was surrounded in its outer zone by outline of fat cells, with no evidence of hemorrhage in the surrounding tissue. In other sections of adrenal glands there were marked deposits of pigment (hemosiderin) and a suggestion of fibrinous deposit, but this was indistinctly visible throughout the section.

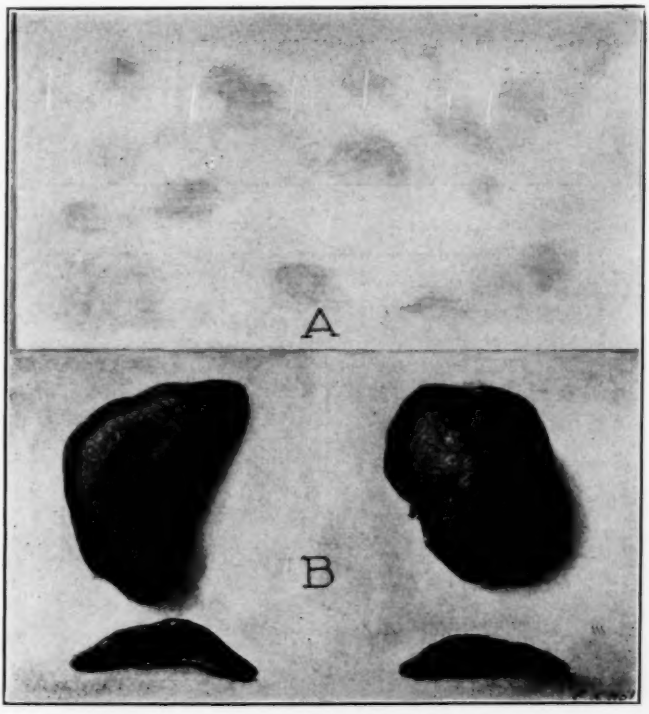

Fig. 1.—*A*, Gross appearance of skin showing purpuric spots. *B*, Gross and cross section of both adrenal glands showing massive hemorrhage.

Skin.—The sections were taken through the purpuric spots of the skin. The stratified epithelium was covered by a very thin layer of keratin. The squamous epithelium showed papillomatous ingrowths into the underlying connective tissue. The connective tissue stroma did not show any microscopic pathologic changes, except for dilatation of the smaller blood vessels but no diffuse hemorrhages.

Bone Marrow.—The section of the bone marrow from the rib showed a rather firm marrow packed with red blood cells, and the surrounding bone was unchanged. There was no evidence of microscopic pathology in the bone or cartilage. In some

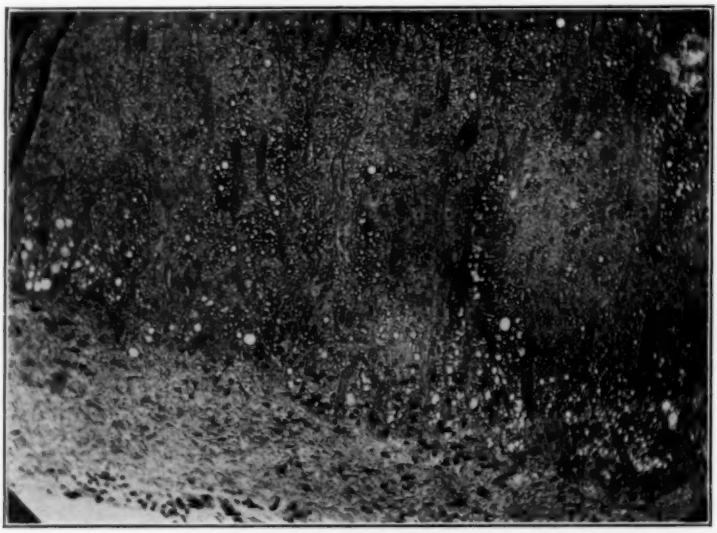

Fig. 2.—Microscopic section of adrenal gland showing hemorrhage with diffuse infiltration of hemoglobin into the cortex and medulla. (×120.)

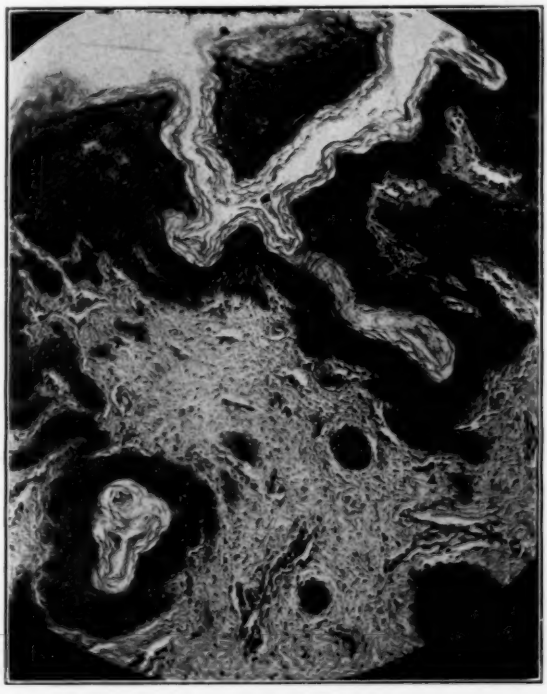

Fig. 3.—Microscopic section of skin through purpuric area. (×96.)

sections the marrow was stained yellow with eosin as compared with other sections of the marrow which took a deep red stain.

Heart Muscle.—The heart muscle fibers showed no unusual microscopic changes.

Thymus gland showed the lobules with the cells uniform in size and the Hassell bodies small and presented no microscopic changes.

Liver.—The central vein and bile capillaries were unchanged. The hepatic cells showed evidences of granular changes in the cytoplasm. The nuclei were more or less of uniform size, a few were swollen, and some of the Kupffer cells, as well as a few macrophages, were laden with brown stained pigment.

Pancreas presented no important microscopic changes.

Kidneys.—The glomeruli were unchanged; the tubules presented indistinct outlines of the cells, some showed granular cytoplasm. The nuclei were more or less of uniform size and placed at the base of the cells.

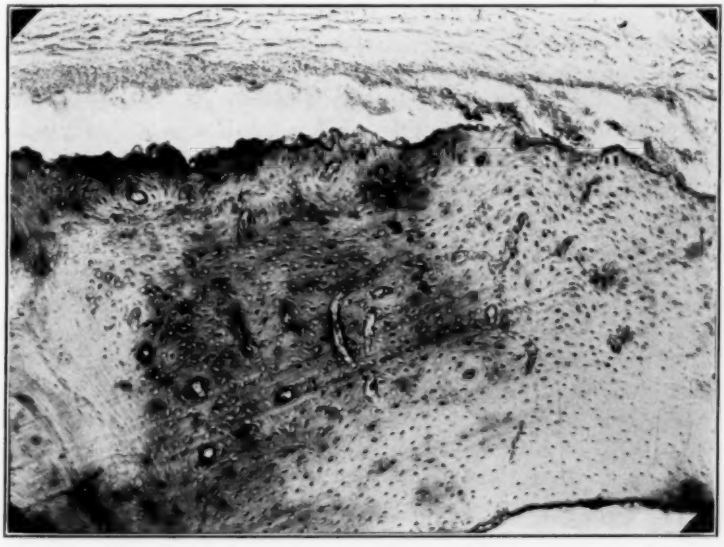

Fig. 4.—Microscopic section through rib showing compact marrow. (×76.)

Spleen.—The Malpighian corpuscles were small and with the splenic pulp presented no unusual microscopic changes.

Lungs showed in one portion of the section a hyperemic area but no evidence of pneumonic foci, and the bronchi were free of foreign material.

Brain.—Sections of the brain showed no microscopic pathologic changes.

DISCUSSION OF PATHOLOGIC CHANGES

The essential pathologic changes in the Waterhouse-Friderichsen disease is a massive hemorrhage in both adrenal glands with purpuric spots on the skin; these invariably are seen at autopsy on these patients. Apparently the hemorrhage in the adrenal gland may be terminal, or it may be the result of the manifestation of a skin purpura or associated with a sepsis.

As a rule, both adrenal glands are somewhat larger than normal and may vary in color from purple red to brown. The hemorrhage may involve the medullary and the cortical portions of the adrenal glands, or the accumulation of fluid blood in the medullary portion may give the adrenal gland the appearance of being dilated and cystic. The microscopic sections of the adrenal gland show a hemorrhagic infiltration from the medullary portion into the cortical portions of the glands. The cells are covered with blood, and the blood vessels are markedly distended and filled with red blood cells. As a rule these dilated capillaries are intact and do not rupture into the surrounding cellular stroma. If one makes special histologic stains using the silver impregnation method for capillaries, one is able to see a markedly dilated capillary network so that the fibrillar framework is separated, and the interlacing network is loosely arranged. Under normal conditions the fibrillar network is more closely compact. The dilated capillaries with a loosely arranged fibrillar tissue lends itself more readily for the diffusion of the blood into the surrounding tissues than would ordinarily take place. It is possible that the spontaneous hemorrhages that occur in the adrenal gland in the Waterhouse-Friderichsen syndrome is associated with congenital weakness of the capillary bed in the adrenal glands. Some authors have called attention to thrombosis occurring in the adrenal gland.

The other characteristic finding in the Waterhouse-Friderichsen syndrome is the petechial hemorrhages that occur in the skin. Histologically one sees a dilatation of the blood vessels in the skin with a more or less diffusion of blood into the surrounding tissue. The appearance of hemorrhage in the skin, particularly around the smaller blood vessels, is interpreted by some as being more of an infiltration of red cells into the tissue stroma rather than a rupture or hemorrhage of the blood vessels causing an accumulation of red blood cells.

Some authors have called attention to the petechial hemorrhages in the serous surfaces of the body. Although this is not a constant finding, nevertheless they may occur. These may be found in the mouth, pharynx, trachea and bronchi, the urinary bladder, conjunctivae, and the endocardium. The mucosa of the stomach and particularly the small intestine seems to be the most prevalent location for these hemorrhages in the internal viscera. Histologically, the mucosa of the gastrointestinal tract shows marked hyperplasia of the lymph follicles and a dilatation of the lymph vessels. The petechial hemorrhages are seen at times on the surface of the mucosa because of the markedly hyperplastic lymph follicles in the intestinal tract. Some authors have attempted to associate this histologic change with early stages of typhoid fever and suggested the relationship of typhoid fever to the spontaneous hemorrhage in the adrenal glands. The mesenteric lymph glands are also markedly hyperplastic.

The spleen presents a very marked hyperemia. Histologic examination shows a marked eosinophilia, as has been reported by Glanzmann. The liver shows pathologic changes similar to that of an acute hepatitis. The hepatic cells present marked fatty changes, the central veins do not show evidence of thrombosis, and the Kupffer cells shows very little changes. Glanzmann noticed an infiltration of eosinophilic leucocytes and focal areas of lymphocytes and polymorphs beneath Glisson's capsule.

The pancreas also shows a marked hyperemia. The bone marrow shows a marked degree of eosinophilic deposits. Bamatter[8] has shown that, when the bone marrow of the ribs is examined immediately after the death of the patient, there is a marked accumulation of myelocytes; whereas, in the peripheral blood smear made during the illness of the patient, this author has demonstrated monocytic macrophages. The degree of degeneration of the cells in the bone marrow is somewhat less than is seen in the peripheral circulation. However, the bone marrow does show evidence of erythropoiesis and myelopoiesis.

The central nervous system presents essentially evidence of marked hyperemia. The cortex of the brain, as a rule, is edematous. Where the meningococcus was an associated etiological factor in the Waterhouse-Friderichsen syndrome, exudative changes take place in the brain. However, in our case in which we have been unable to demonstrate any causative organism in the blood or tissue, we have not been able to demonstrate any suppurative changes in the brain, and found only a hyperemia. The histologic examination of the pharynx, larynx, heart muscle, trachea, bronchi, and kidneys may show in some cases evidence of hyperemia with focal deposits of leucocytes, but nothing characteristic in these organs that would be in keeping with the picture of spontaneous adrenal hemorrhage and purpura.

CLINICAL PICTURE

Spontaneous hemorrhage into both adrenal glands associated with purpura may occur in children between two months and two years of age. As a rule these children are usually healthy and are breast fed. At times prodromal symptoms, as fatigue, may occur twelve or twenty-four hours before the appearance of the skin eruption. The child appears pale and may have a slight elevation of temperature. The usual history is that of a sudden onset when the child is awakened suddenly by crying. This may be followed by vomiting and then the appearance of diarrhea with pain in the abdomen. No pus, blood, or mucus, as a rule, is seen in the stools. At times convulsions of a tonic-clonic nature may present themselves. The child may be conscious during these attacks, or he may go into a state of coma. Purpuric spots develop on the skin, and these are irregular, flat, or star shaped and may cover all parts of the body. These eruptions may coalesce to form larger areas and may

present a cyanotic or a blue-red appearance to an almost black color. Seldom is the mucus membrane involved. These eruptions on the skin have frequently been associated with Henoch's purpura.

At the onset of the skin eruptions the child goes into a state of collapse. The heart rate is slowed, and the blood pressure usually drops. The body feels warm, but the extremities are cold. The pulse is elevated at times to 200, and it is weak and irregular. A marked cyanosis of the skin develops, and the child lies in bed with the eyes half shut. Respirations are rapid and shallow, and as the condition progresses the child develops a Cheyne-Stokes type of respiration. Examination of the lungs does not reveal any unusual findings, but later in the course of this condition, dyspnea with dilatation of alae nasi becomes more marked, and râles are heard at the bases of the lungs. Examination of the abdomen may reveal a soft, slightly distended abdomen; seldom is pain elicited on pressure; and there is no evidence of hemorrhage in the abdomen. The child later becomes more and more sleepy and comatose; convulsions with a sudden elevation of the temperature take place just before death. The spinal fluid is negative. Death takes place anywhere from six to twenty-four up to forty-eight hours after onset of symptoms.

A great deal of emphasis has been placed on the blood picture in the Waterhouse-Friderichsen disease. In Rabinowitz's case[9] there was a leucocyte count of 7,400 with a differential count of 76 per cent polymorphonuclear leucocytes; 20 per cent lymphocytes, and 4 per cent monocytes. The blood platelets although present, were not increased in amount. This author is of the opinion that hemorrhage in the adrenal glands and purpura is associated with a thrombopenic state.

Glanzmann believes that there are three phases of the blood picture that occur in the Waterhouse-Friderichsen disease. In the first phase there is a progressive and excessive thrombopenia until no platelets are seen. In the second phase there is an alteration of the white blood cells with a particular diminution of the polymorphs. The leucocytes might go up to 12,000. The polymorphs show degenerative changes so that they appear as outlines of cells, and may undergo further degenerative changes to a degree that they appear as dust particles. These particles may coalesce and form larger particles. Some of the polymorphonuclear cells show vacuoles in the cytoplasm. The nucleus may show degenerative changes, or they may become disintegrated and show vacuoles. The eosinophiles, although not diminished in number, show vacuoles. The small lymphocytes show a diminution in the amount of protoplasm. There is an increase in the monocytes. The third phase consists of a marked anemia with erythroblasts due to an infectious stimulation of the bone marrow. There is a basophilic stippling and a polychromatophilia. The bleeding time is about 15 minutes, clotting time 5 minutes, and clot retraction zero.

The blood chemistry examinations were performed by various authors in only a few cases. Baumann[10] and Bamatter[10] among others have shown that there is usually a diminution in the blood sugar and that the nitrogen partition is elevated. Henning-Magnusson[10] showed further that the calcium content in this syndrome is between 10.7 and 10.8 mg., and the inorganic phosphorus 5.2 and 5.4 mg.

ETIOLOGY

From the very earliest reports the Waterhouse-Friderichsen syndrome has been associated with some form of an infection. Voelker[11] and Andrewes[12] were of the opinion that the purpuric spots simulated smallpox. Most of the cases reported of Waterhouse-Friderichsen syndrome did not, however, occur during a smallpox epidemic. Ikeda[13] believed that the purpuric spots on the skin might be associated with hemolytic streptococcus infection. It was this author's opinion that the hemolytic streptococcus or its toxins may attack the leucocytes or the red blood cells with a subsequent destruction of these cells thus leading to a purpuric state. In the twelve cases which were autopsied by Friderichsen, seven gave sterile cultures. In Glanzmann's case cultures of the heart's blood and spleen were sterile. On the other hand, Dudgeon[14] isolated *Staphlococcus albus* and pneumococcus. Little isolated a streptococcus. MacLaglan and Cooke[15] in a case of malignant cerebrospinal fever noticed hemorrhage in both adrenal glands, and they were able to isolate the meningococcus.

PATHOGENESIS

It seems to be the opinion of most of the authors who have reported their findings in the Waterhouse-Friderichsen disease that this syndrome is associated with a sepsis in spite of the sterile cultures obtained in vivo or after death. Some authors are of the opinion that infection of the liver or spleen may result in an anaphylactic reaction. This opinion is evolved from the observations made of histologic examination of the liver in which was noticed an infiltration of eosinophiles, lymphocytes, plasma cells, and a few polymorphs beneath Glisson's capsule. Further evidences of an anaphylactic reaction which involves the liver are based on studies made by Schottmüller and Fahr,[16] who studied the proliferative hepatitis which occurs in scarlet fever. Furthermore, the opinion has been propounded that anaphylactic toxins and poisons attack the adrenal glands because of the immediate vascularity of this organ. In children the adrenal glands are exceptionally sensitive to vasodilator substances. The capillaries rupture easily in the adrenal glands, partly because of their thin walls and also because of lack of secretions from other glands of internal secretion which may alter the tonicity of the blood vessel wall. In other instances the so-called anaphylactic toxin may be a capillary toxin which attacks the blood vessels in the adrenal glands.

In physiologic hemorrhage of the adrenal gland in the newborn infant and in older infants skin purpura does not develop; nor is there any manifestation of purpuric hemorrhage when there is a thrombus in one of the adrenal glands. Experimentally, the removal of both adrenal glands does not lead to a hemorrhagic diathesis. The opinion of Thomas[17] that there is a subacute infection with hemorrhage in the adrenal glands, and later hemorrhage into the skin, is not plausible for the reason that in acute insufficiency of the adrenal glands the skin appears to develop an increased resistance toward histamine or histamine-like substances.

Finally, Baumann believes that there is a constitutional disposition such as might exist in some types of endothelial diathesis (Bayer). In Glanzmann's case the child's mother had frequent nosebleeds and tuberculosis.

DISCUSSION

The early reports of adrenal apoplexy in children appeared in the English literature. In fact, Little believed that there was a similarity between the causative factor of this disease and that in Addison's disease with skin pigmentation. It was in 1911 when Waterhouse presented the clinicopathological syndrome of spontaneous bilateral hemorrhage in both adrenal glands with skin purpura. His studies were based on observations of 15 children between the ages of two and fifteen months who died following an illness of twenty-four to forty-eight hours. With the exception of three cases, all showed a purpuric rash on the skin with adrenal hemorrhage. This syndrome was accompanied by vomiting, diarrhea, convulsions, abdominal pain, and tracheobronchitis with a slight elevation of fever. Seven years after Waterhouse's report, in 1918, Friderichsen gave detailed characteristic clinical pictures of three of his own cases which he had observed personally and of twenty-five he had collected from the literature. Since then there have been various reports of the Waterhouse-Friderichsen syndrome. Aegerter in 1936 collected 55 cases from the literature and reported two of his own. Since Aegerter's report single cases have been reported by Kamber[18] and Usher.

That the Waterhouse-Friderichsen syndrome is not uncommon is seen from the cases which have appeared in the literature. In addition, it is possible that a number of cases have been overlooked, either clinically or on the autopsy table. For example, one must differentiate between the hemorrhage in the adrenal gland which may occur as a physiologic condition in the newborn infant, and traumatic hemorrhage of the adrenal gland which may be the result of birth trauma in infants. These two conditions may not be associated with purpuric spots of the skin. Some investigators believe that spontaneous massive hemorrhage in both adrenal glands with skin purpura may be associated with a

constitutional disfunction. They have noticed this condition in infants, who have had an enlarged thymus and hyperplastic lymph follicles with hemorrhage into the intestinal mucosa. In fact, Rabinowitz mentioned that status thymicolymphaticus may be associated with an insufficiency of the chromaffin system.

Those who have been able to observe this syndrome clinically have reported hypotension, low blood sugar, flaccidity of the muscles, vomiting, diarrhea, abdominal cramps, and circulatory collapse, and believe that these may be due to a functional disorder of the adrenal glands. Rogoff,[19] however, states that experimentally the animal may suffer a loss of both adrenal medullas and one cortex without radically influencing his life and health, and there is no good evidence that epinephrine plays a role in the maintenance of normal blood pressure. Loeb,[20] on the other hand, demonstrated that the adrenal gland may exert an influence on the metabolism of the sodium ion, depleting the blood of both sodium and chloride, and that there is an accompanying dehydration in the kidneys (hypoadrenalism). The death that occurs in Waterhouse-Friderichsen disease takes place too rapidly for these changes to take place and be the causative factor in death. In fact sodium metabolism studies have not been determined as yet in this syndrome.

Many authors have demonstrated bacterial invasion of the blood stream in the Waterhouse-Friderichsen syndrome while others were unable to do so. Although the organisms may not be demonstrated, it is possible that their toxins may be the agent causing purpuric spots on the skin and hemorrhage in the adrenal glands. Aegerter believes that the meningococcus is the sole cause of the Waterhouse-Friderichsen syndrome, and he feels that only accurate bacteriologic methods employed in a large series of cases will still this question. This statement may be questioned for the reason that the organism is not difficult to demonstrate by smear or culture, and the fact that the Waterhouse-Friderichsen syndrome is not necessarily associated with epidemics of the type due to a meningococcus. Why there should be a selectivity of the adrenal glands and the skin more so than any other organ in the body by the meningococcus is a question for further investigation. It is true that the changes that occur in other organs in the body may be changes associated with a sepsis, but this in turn may be due to organisms other than the meningococcus.

From the standpoint of diagnosis, the Waterhouse-Friderichsen syndrome must be considered in all infants and young children who become acutely ill with vomiting, diarrhea, a shock syndrome, and collapse. Because of the fact that the Waterhouse-Friderichsen syndrome is invariably fatal, the duration from the onset of symptoms until death does not give the attending physician a sufficient opportuntiy to insti-

tute remedial measures. Few clinicians who have recognized the disease early have tried adrenalin intramuscularly and intracardially, as well as intravenous injections of sodium chloride. If the meningococcus has been isolated, the antimeningococcus serum has been given. However, the prognosis as indicated by most of the cases reported in the literature is that it is universally fatal.

CONCLUSIONS

The syndrome known as the Waterhouse-Friderichsen disease is accompanied by a sudden onset of malaise, vomiting, diarrhea, fever, rapid pulse, cyanosis, purpuric spots on the skin, lethargy, coma, and death. This disease is usually fatal from twenty-four to forty-eight hours after the onset of symptoms. The etiology is not definitely known although there are many who believe that this disease may be associated with a bacteriemia or a toxemia. The essential pathologic findings consist of massive bilateral hemorrhages in the adrenal glands with purpuric spots in the skin. We have reported such a case which we have observed on the autopsy table.

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SAW-TOOTH FEVER PNEUMONIA

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IN 1928 E. Moro[1] described a type of pneumonia to which he gave the name *Sägefieberpneumonie*, which was characterized by intense and persistent consolidation of one lobe, intermittent fever with very wide daily variations of temperature, a very protracted course, and a good prognosis. Moro reports six such cases, all in the age group 1 to 2½ years. In addition to the consolidation of one lobe, there were fleeting consolidations of other lobes in all cases except one. The course in the hospital varied from 26 to 73 days, in all cases preceded by several weeks of illness in the home. Tuberculosis was excluded by a negative Pirquet reaction in every case. The daily variations in temperature were generally much more marked than those commonly seen in so-called septic fever, a difference of 10° F. being repeatedly recorded on the charts published with Moro's article. In spite of the high fever and the protracted course, all the children recovered without complications. The termination of the fever was critical, in that one of the marked daily remissions was followed by permanently normal temperature.

External circumstances prevented the taking of routine roentgenograms, but the physical findings convinced the author that he was dealing with pneumonias of the lobar type. Blood cultures were not taken, but the absence of all complications was considered as evidence that true septicemia was not present. The author is inclined to regard the marked swing of the temperature curve as a daily pseudocrisis.

This opinion as to the nature of the marked daily variations in temperature is shared by Freudenberg,[2] who in a brief communication discusses some cases of this type of pneumonia. Of 467 cases of pneumonia admitted during a period of ten years, 10 were of this type. On the whole they belonged to the same age group as the cases described by Moro; one patient was 6 months old; three were about one year, three, 2-3 years, three, 3-4½ years. All except one case proved by x-ray pictures to be pneumonias of lobar extension, the exception being described as confluent bronchopneumonia. Freudenberg, as well as Moro, emphasizes the slow spread of the pneumonic process, in that in some cases several weeks elapsed before definite physical signs were elicited. Mild pleural involvement, demonstrable only by x-ray, was present in all but three cases. In no case did empyema or other complication occur, and the outcome was invariably complete resolution. The clinical picture was dominated by the daily occurrence of a critical fall in the tem-

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perature, sometimes leading to collapse; often, however, as also emphasized by Moro, the condition of the patients was surprisingly good during the remissions.

In Wiskott's monograph on childhood pneumonia[3] numerous cases with saw-tooth fever are included. These, however, were of shorter duration than those described by Moro and by Freudenberg, and the latter author feels that cases of only ten to twenty days' duration should not be included in the diagnosis of saw-tooth fever pneumonia. The age-group of Wiskott's cases was the same as in the cases reviewed above; the fever terminated by crisis; complications did not occur; and the prognosis was good. The pneumonias were either lobar or marginal, not (on the roentgenogram) extending in to the hilum. The course was, generally, somewhat longer than in the typical lobar pneumonia. Wiskott places these cases in his group of "transitional" pneumonias, the transition being from the "primitive," diffuse bronchopneumonias of the young infant to the "mature" more circumscribed bronchopneumonias and lobar pneumonias of the older child. The only difference between Wiskott's cases and those previously described is the shorter duration of the illness, the longest duration in his recorded cases being twenty-three days.

It seems, then, that an unusual type of temperature curve may occasionally be seen with pneumonia in children of this age group and that, when this type of fever is present, the prognosis is usually good in spite of the course which is generally of long duration. We have had the opportunity to observe two cases of this kind, which will be briefly described.

CASE 1.—G. C., white male, 18 months old, previously well, was admitted because of fever, vomiting, and cough. One month previously the child had measles with a rash of three days' duration. He was kept in bed for one week, but continued to have a fever and appeared ill. The last few days before admission the child vomited frequently, and the respiration was labored. The night before admission the temperature was 106° F.

On admission the child was acutely ill, irritable, and slightly cyanotic. There were dullness and tubular breathing over the left base, and a roentgenogram of the chest showed, indefinitely outlined, a triangular area of increased density behind the heart, a lesion which later increased in size and extended outside the border of the heart.

The further course was characterized by an intermittent temperature with extremely wide daily variations (Chart 1). This temperature naturally aroused the suspicion of a septic condition, but a blood culture taken on the fourth day after admission showed no growth. A throat culture taken on the sixth day showed pneumococcus Type XIV and *Staphylococcus albus*. Tuberculin intracutaneously in dilutions 1:1000 and 1:100 gave no reaction. The white count was between thirty and forty thousand, with a predominance of polynuclear leucocytes.

On the ninth day after admission the condition culminated with a temperature drop of over ten degress, and from then on the child was free from fever and improved rapidly. However, the physical signs over the chest persisted, and for that reason a puncture was made in the dull area on the left base; 8 c.c. of sero-

sanguineous fluid was obtained, and culture of this fluid showed no growth. Eight days after the final crisis x-ray examination of the chest showed an area of consolidation even larger than previously, but because of the good general condition the child was discharged. On a subsequent examination in the out-patient department the child was found to be doing well.

CASE 2.—N. F., 2½-year-old white male, was admitted because of a cold and swollen cervical glands. About three weeks previous to admission the child developed a cold, and one week later swelling of cervical glands was noted. This swelling disappeared in a few days, but reappeared five days previous to admission. At this time the child developed another cold, and had some fever the last day before admission.

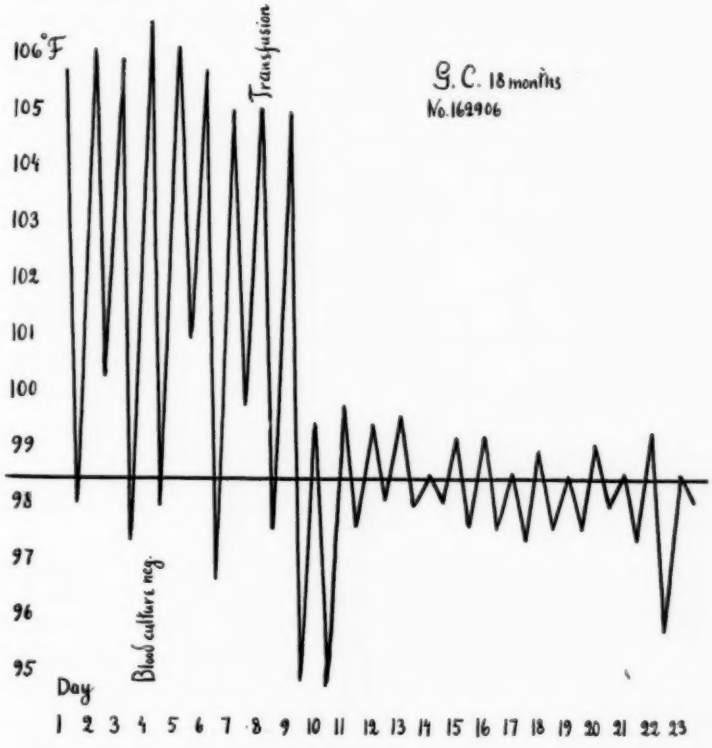

Fig. 1.

On admission the child was not very ill. The throat was red, there was some postnasal discharge, and the cervical glands were enlarged on both sides. The temperature was 102.7° F. A throat culture showed a mixed flora with green-producing streptococci predominating (no hemolytic streptococci). Tuberculin intracutaneously in dilution 1:1000 was negative.

During the first week in the hospital the temperature was, on the whole, lower than on admission, but reached 103.2° F. on one occasion (Chart 2). On the eighth day the temperature began to assume a spiking character, getting increasingly higher every day for a few days. This type of fever lasted for nine days. A

few days after it began, signs of pneumonia were found on the left base, a finding confirmed by x-ray, which showed a pneumonia of nearly lobar extension in this locality.

The day after this pneumonia had been found the child developed an otitis media; both ears were opened, and there was purulent drainage from the right. A culture of the pus showed green-producing streptococci.

During the period of spiking temperature, three blood cultures were taken; one showed *Staphylococcus aureus*, but this was considered a contamination, as the other two were negative. A throat culture taken at this time showed a few green-producing streptococci, a few staphylococci and a bile-soluble pneumococcus which was not of Type I, II, III, V, VII, or VIII. Agglutinations against paratyphoid A and B, typhoid, and brucella organisms were all negative. A spinal puncture showed normal fluid under normal pressure, from which no growth was obtained. The white count rose from 18,050 on admission to 55,000 on the sixth day after the onset of the high, spiking temperature.

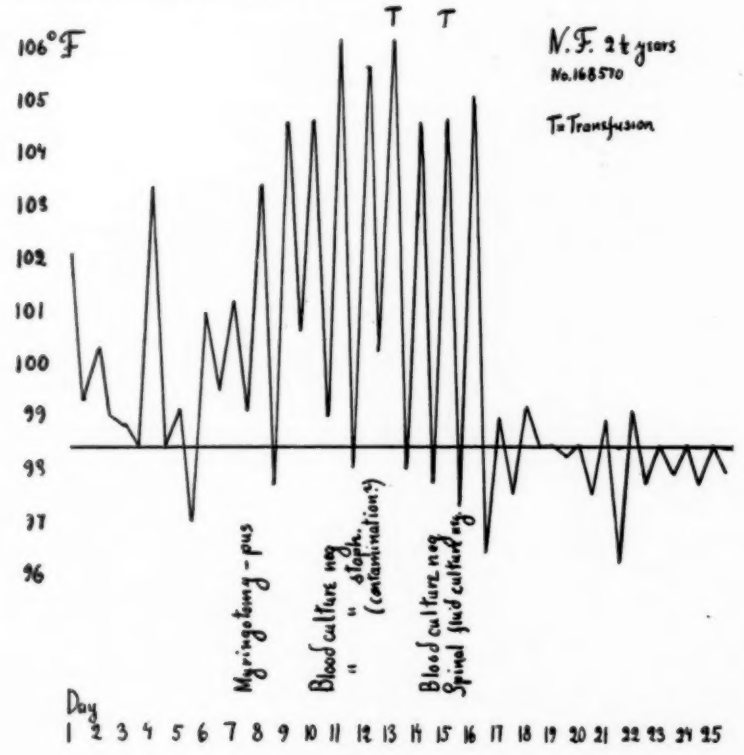

Fig. 2.

Nine days after the saw-tooth fever began, the temperature abruptly became quite normal. The child was kept in the hospital for ten days longer and was then discharged, clinically well, although some dullness still persisted on the left base.

Both of these cases showed the saw-tooth type of fever, the first with an average daily swing of 7.5° F., the second of 8.0° F. Both of them had a history of preceding infection (measles in Case 1, cervical adenitis in Case 2), but, although the history would suggest a secondary bronchopneumonia, the x-ray films in both cases showed a single, fairly extensive focus of consolidation. Pneumococci were isolated from the throat in both instances, although not in pure culture, and the significance of this finding may be questionable.

Although cases of this kind are rare, they are of practical importance and, perhaps, of some theoretical significance. As the physical signs of pneumonia may be slow in developing, there may be a period when the swinging temperature is the only abnormal finding, and it may be well to know that in children of this age group, fever of this type may be associated with pneumonia. After the pulmonary consolidation has been found, a knowledge of the good prognosis may give some confidence to the attending physician in a rather harassing situation.

As to the theoretical significance of this type of fever in pneumonia, it might be, as assumed by Wiskott and by Freudenberg, that it indicates a special state of reactibility. In the young infant the pneumonias are, generally, diffusely spreading, and a definite circumscribed shadow in the x-ray picture is, perhaps, more likely to be caused by atelectasis, a foreign body, or aspiration, than by a pneumonia in the strict sense; while later on, we are beginning to see more of those pneumonias which are localized in one or more foci, the "battlefield" pneumonias of Wiskott. It seems probable that this change in the clinical picture as the infant grows older is due to a changing immunologic response; and it is possible that saw-tooth fever in pneumonia is an expression of some intermediate form of reactibility.

SUMMARY

Two cases of pneumonia with extremely wide daily variations in temperature are reported. They conform in many respects to the picture of saw-tooth fever pneumonia described by Moro and by Freudenberg.

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CALCIFIED HEMATOMA

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ACCORDING to Kidner,[1] in 1917 there were five theories for the formation of calcified hematomas, all of which had warm supporters and antagonists. The first theory supposes that the hemorrhage following an injury to muscle is first transformed into cartilage, which later ossifies. The second is that the tumors are aberrant sesamoid bones; the third, that the growths result from bits of periosteum detached and included in the muscle; fourth, that the fibrous tissue of the muscle undergoes a true metaplasia into bone; and fifth, that the ossified area develops from cells disseminated from the periosteum through the hemorrhage. He modifies the latter slightly in his own theory, which is that trauma to the bone tears deep muscle fibers and at the same time causes a break in the periosteum. From both sources, blood is poured out, and immediately deeper layers of periosteum respond to the stimulus of trauma by pouring forth osteoblasts. These cells are free to wander through the mass of hemorrhage, and from all directions bone growth begins.

Gessner,[2] in reporting two cases in 1924, agreed with Kidner's theory. On the other hand, Bullitt[3] in 1927 assumed that bone formation in the skeletal muscles, if of traumatic origin, is not necessarily derived from misplaced periosteum, but may be heterotopic ossifications, which are genetically the same as true bone formations in the kidneys, lungs, aorta, or in scars of muscle.

In the same year Seeliger[4] suggested that extravasations of blood from the subcutaneous tissue are followed by an immigration of mesenchymal elements with vascular offshoots along the reticulum of fibrin developing within a few days from the blood effusion. The red cells lose their form and colorability and gradually disappear. At this stage fibroblasts, histiocytes, plasma cells, leucocytes, and a few lymphocytes are to be seen. Eosinophiles are also fairly numerous. Fibrin formation then begins and the cellular elements give place to the formation of pure connective tissue. In many cases an extensive effusion may be entirely absorbed. Intramuscular effusions develop into connective tissue in much the same way. In some cases, lime salt deposits appear in the connective tissue lying between the disintegrating muscle fibers.

It is a well-known pathologic anatomical fact that upon the basis of tissue impairment lime salt deposits appear in the injured portions

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and sufficient enrichment of the calcium salt content in the course of the process of organization may lead to true bone formation.

According to Aschoff, cited by Seeliger, a deposit of lime must involve (1) an organic substance with a strong affinity for calcium, (2) a high calcium content in the blood and humors, and (3) a change in the rapidity of the blood current. The first step in calcification comprises the combination of calcium ions. New callus tissue must first absorb calcium and afterwards phosphoric acid and the corresponding carbonic acid. The second step is the accumulation of phosphorus in the calcifying or ossifying tissue. The third step depends upon the metabolism of fats or proteins. Albuminous products have a strong tendency to unite with calcium, forming complex combinations. Two-thirds of the dissolved calcium in the body is dissolved in the blood serum, while one-third exists in combined form in the albumin of the serum.

The quantity of calcium in solution depends upon the concentration of hydrogen ions and increases with any augmentation of acidity in the calcium ion content. The hydrogen ion concentration is increased wherever inflammation occurs and wherever dead tissue appears. The dead tissue has a relatively high alkalescence, while the surrounding tissue develops a high acidity. The union of calcium with dissolved or undissolved albumin increases with the augmentation of alkalescence. Since in consequence of the heightened alkalinity the calcium content is greater in the inflamed surrounding region, the necrotic tissue is enabled to absorb lime from this region up to the saturation point. If phosphorus is present in a condition favorable for reaction and if the albumin is decomposed, the conditions requisite for calcification are afforded.

In 1930 Magliulo[5] found in a series of cases of direct trauma to muscles that a hematic effusion always preceded the calcareous or bony formations. The calcification did not always turn into ossification, but on the other hand there were no cases where the ossification set in without being preceded by calcium deposits. He concludes that, while a hematic effusion may give rise to calcifications, this does not represent the principal and absolute coefficient for the neoformation of bone after trauma. Other factors, such as environment, extension, and degree of original trauma of muscles, amount of calcium in the blood, modifications arising from treatment, etc., must be reckoned with.

The following year, von Brand and Holtz[6] showed by experimentation that local calcifications may be produced by a subcutaneous administration of irradiated ergosterin and that these calcifications were not conditioned by inflammatory processes, but were the result of a specific effect of a transformation product of the ergosterin.

Tumpeer and Denenholz,[7] in 1936, reported calcium deposition in a newborn infant with tetany, following the intramuscular injection of whole blood from the father and four injections of calcium intramuscularly, three in the form of the gluconate and one in the form of the levulinate. Chemical analysis of a small bit of material from one buttock, after sloughing took place, revealed the deposit to be in the form of calcium phosphate. After four months of conservative treatment these deposits had practically disappeared. Their explanation for the deposition is that soluble calcium may cause a coagulation of tissues in patients with the disturbed calcium metabolism of tetany. Calcification in the blood vessels would account for the necrosis and sloughing, typical of gangrene. In diffusing through the fascial planes, the blood phosphate apparently fixed and precipitated the calcium in the form of calcium phosphate.

Von Hofe and Jennings,[8] also in 1936, reported a case of calcium deposition following the intramuscular injection of calcium gluteally. This patient developed an abscess on one side, which healed after surgical incision and drainage. X-ray films after six months revealed no evidence of calcium deposit. These authors considered the possibility of myositis ossificans traumatica and injected normal saline into muscles of the right arm. The patient was observed for one month, but no calcification or induration appeared.

CASE REPORT

The patient, a colored infant, U. H. No. 13776, was admitted to the Hutchinson Memorial Clinic on March 15, 1938. The baby was born on Feb. 22, 1938, and three days after birth began to have hematemesis and melena. There were no other evidences of hemorrhage. He was brought to the clinic where he was given 15 c.c. of whole blood (from maternal grandmother) intramuscularly in both gluteal regions. He was immediately sent into Charity Hospital and on the following day was given 70 c.c. of citrated blood intravenously. The infant bled through both the anus and mouth for about 16 hours after admission, after which there was no further bleeding. At the age of three weeks, when the baby was brought back to the clinic, a hard indurated swollen area was found on the left buttock at the site of injection of whole blood. This mass was about 3 by 3 cm. and in the center there was a small necrotic area from which a slight amount of whitish grey purulent material was exuding. (Smear revealed only a few pus cells and no organisms.) The muscles of the right thigh were increased in size, hard, and somewhat tender. The skin overlying was shiny, tense, and bluish black in color. Blood count at this time was as follows: red blood cells, 3,510,000; hemoglobin, 70 per cent; white blood cells, 12,000; small lymphocytes, 47 per cent; neutrophiles, 49 per cent. There was a history of occasional vomiting, and the baby appeared to be very irritable, crying during the length of the examination. A surgical consultant reported on March 17, 1938, as follows: "Evidently two organizing hematomas, which may also be ossifying." X-ray examination on March 19, 1938, revealed a slight increase in density in the region of the soft tissues of right femur and left buttock, suggestive of calcified hematoma. At the suggestion

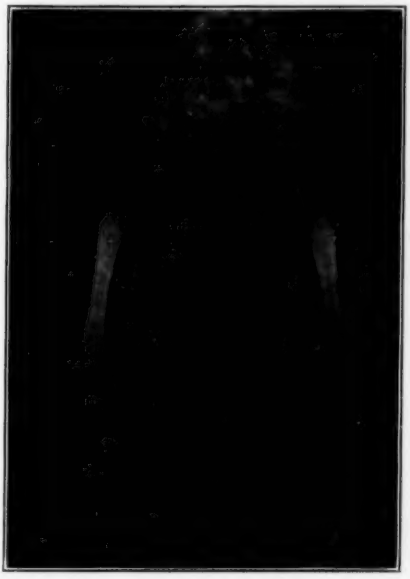

Fig. 1.—The calcified hematoma may be seen involving most of the right thigh posterior to the femur.

of one of the staff members, the patient was hospitalized, where he was given physical therapy in the form of radiant heat over both buttocks. On March 28, 1938, the hardened areas had decreased somewhat in size and x-ray examination May 11, 1938, reported that there was marked absorption of opaque material previously noted.

COMMENT

Notwithstanding the several theories which have been advanced as to the cause of calcified hematomas, the thought came to us that the calcium content of the donor's blood might have been a contributing factor. However, the blood calcium was 9.8 mg., while the phosphorus was only 3.3 mg. On admission, because of the precarious state of the infant, our efforts were concentrated on controlling the bleeding, and no blood chemical studies were done.

Prior to 1926 all of these calcified hematomas were treated by surgical removal. However, C. A. Stone,[9] at this time treated two cases by heat and massage with definite improvement. We decided to try this form of treatment first, and our results seemed to be in accord with those obtained by Stone.

SUMMARY

A case of calcified hematoma is reported.

Theories of the underlying cause of this condition are enumerated.

From the meager literature, apparently calcified hematomas do not occur frequently following the intramuscular use of blood, and the few that do occur do not seem to constitute a contraindication to the use of this valuable therapeutic measure.

Treatment by physical therapy seems to have merit and should be tried before surgical intervention.

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SYNDROME OF CONSTRICTING DOUBLE AORTIC ARCH IN INFANCY

Report of a Case

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DOUBLE aortic arch can produce unfamiliar but characteristic symptoms which are misunderstood and misinterpreted until necropsy clears up the diagnostic puzzle. Inasmuch as but few cases have been reported, it seems worth while to record another instance for the purpose of directing clinical attention to the anomaly.

L. H., a white male infant, was born at full term, weighing 6 pounds 2 ounces. Labor and delivery were uncomplicated. At 6 days of age he was weaned to a cow milk formula and given orange juice and cod liver oil. The family history was negative.

Ever since birth he breathed with a constant stridor and had a peculiar grunting, hoarse cry. Paroxysms of coughing associated with dyspnea and stridor would occur during feedings. It was noted also that he preferred to lie with his head in an extended retracted position, although the neck was not rigid and could be readily flexed without discomfort.

Because of these symptoms the diagnosis of thymic hypertrophy was made, and the infant was referred to the Out-Patient Department of the Children's Memorial Hospital, Chicago, for treatment. When he was first seen at the hospital at 6 weeks of age, the harsh stridor was very noticeable, and dry inspiratory rhonchi were audible in all parts of the chest. Roentgenogram of the thorax demonstrated a broad enlarged upper mediastinal shadow, 3.5 cm. in width. Four x-ray treatments of 40 R units each produced no detectable alteration in the radiologic appearance of the chest.

The next examination note, made at 4 months of age, stated that the child could sleep quietly without noisy breathing but that during activity or crying a high-pitched crowing respiratory sound became audible. There were occasional gasping spells especially during feedings.

At 4½ months the child was admitted to the ward for special care because of restlessness, fever, anorexia, stridor, and cough. Physical examination showed bilateral otitis media, râles at both lung bases, and loud rhonchi arising in the large bronchi. Dyspnea with cyanosis appeared some days later, requiring oxygen therapy. Bronchial breathing, bronchophony, and percussion dullness became apparent in the right lower lobe posteriorly, and later on the left side. Eight days after admission respirations ceased unexpectedly during feeding. A roentgenogram taken post mortem showed no changes in the upper mediastinum and diffuse bronchopneumonic clouding of the lungs. The clinical diagnoses were congenital laryngeal stridor and bronchopneumonia.

Necropsy Findings.—The body was well developed and free from gross anomalies except in the great vessels over the heart. The lungs were the seat of acute bilateral bronchopneumonia. The liver and spleen were congested. The thymus was small, weighing but 5 gm.; its microscopic appearance was one of extreme atrophy with small shrunken lobules. The mediastinal tissues were not fibrotic. The other viscera

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displayed no striking changes. Rickets was not present. Pneumococci were grown from the heart's blood and the left lung. The right lung yielded many colonies of pneumococci and a few of *Micrococcus catarrhalis.*

The heart was situated in its customary position with apex in the fifth left interspace. The left atrium was contracted and empty wheras the right was dilated and engorged. The foramen ovale was completely occluded, and the valves, septa, and coronary vessels all appeared normal. The chamber of the right ventricle was dilated, and its wall seemed a little hypertrophied, measuring 3 mm. in thickness. The left ventricle, not dilated, measured 6 mm. in wall thickness.

Two superior venae cavae were present, lying anterolateral to the great arterial tubes. The one on the right entered the upper part of the right atrium in normal fashion, whereas the other curved behind the left atrium to empty into the distal tip of the coronary sinus. The presence or absence of a transverse anastomosing vein was not noted. The small coronary veins entered the enlarged but otherwise normal coronary sinus in the usual fashion. The inferior vena cava was not anomalous nor reduplicated.

The aorta arose from the left ventricle in the normal manner passing upward, forward, and to the right of the pulmonary ring. Two centimeters above its origin the aorta divided into two branches, a right and a left, which coursed on either side of the trachea and esophagus and reunited posteriorly to form the descending aorta. The left aortic branch seemed a little narrower, measuring 6 mm. in diameter after formalin fixation, whereas the diameter of the right arch was 8 mm., and of the ascending aorta, 1.2 mm. The left branch showed the usual relations of the aortic arch, passing diagonally in front of the trachea and over the left main bronchus. The right branch crossed the right main bronchus and ran obliquely behind the esophagus. These aortic arches encircled the trachea and esophagus in a snugly fitting arterial collar which measured approximately 1 cm. in internal diameter. The diameter of the trachea was 1 cm. throughout except where the lumen became somewhat constricted anteroposteriorly while passing through this ring. The outer coat of the esophagus was congested here. Neither the trachea nor the esophagus was dilated or otherwise abnormal above or below the aortic ring.

Just at the bifurcation each aortic arch gave rise to its common carotid artery, these two trunks arising but 3 mm. apart from each other. A few millimeters beyond these lay the symmetrically placed origins of the subclavian arteries. The fibrosed ductus arteriosus was situated in its normal position, running down from the under surface of the left arch just beyond the left subclavian to join the pulmonary artery above the bifurcation of the latter. The ductus was 6 mm. in length and 4 mm. in thickness; its lumen was obliterated.

The descending aorta measured 1 cm. in diameter in the upper thoracic region. Its position with respect to the vertebral column was not noted.

The vocal cords and other structures in the larynx were free from gross changes. The laryngeal nerves were not dissected.

The pathologic diagnosis was double aortic arch, encircling and compressing the esophagus and trachea; bilateral superior venae cavae; atrophy of thymus; bilateral bronchopneumonia (pneumococcal); acute circulatory congestion of liver and spleen.

DISCUSSION

Aortic arch malformations are not familiar to clinicians, with the exception of coaretation, since physiologic disturbances are usually not produced. The more common aortic arch anomalies are right-sided aortic arch with left-sided innominate artery; right-sided aortic arch with an aortic diverticulum behind the trachea, representing a persistent left aortic root, from which the left subclavian artery and the ductus

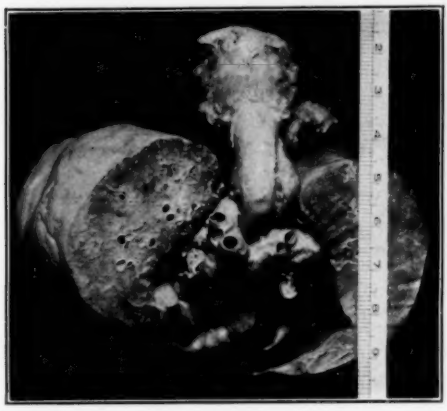

Fig. 1.—Anterosuperior view of post-mortem specimen. The ascending aorta bifurcates into the right and left aortic arches, which together form a collar closely encircling trachea and esophagus. Food material passing down the esophagus produced temporary collapse of the tracheal lumen.

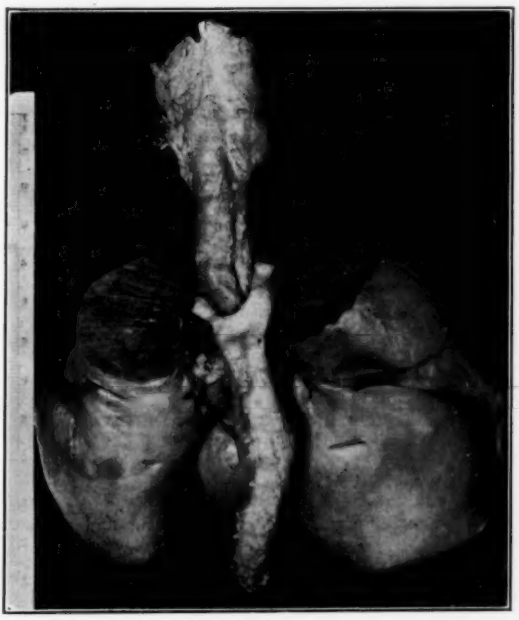

Fig. 2.—Post-mortem specimen. Posterior view, showing reunion of right and left aortic trunks behind esophagus and trachea. The greater size of the right trunk is clearly evident.

arteriosus arise; right subclavian artery arising from the distal portion of the normal left arch instead of from the right innominate, and running posterior to the esophagus; complete atresia of the transverse part

of the left arch; coaretation (isthmus stenosis) of the left aortic arch; persistent double dorsal aorta; double aortic arch.

In the very young human embryo there is a series of primitive aortic arches through which blood from the heart flows to the thoracic aorta. The normal adult aorta is derived from the fetal fourth left aortic arch. "Doubling" results from failure of involution of the fourth right aortic arch; the ascending aorta bifurcates in front of the trachea and its branches reunite behind the esophagus. Sometimes the left arch becomes obliterated and may disappear, leaving the persistent right arch to convey the blood stream.

From the anatomic standpoint much has been written concerning the mechanisms at work in the normal development of the embryonic aortic arch system.[1, 2] The various malformations which can occur are usually classified morphologically in terms of the persistent aortic arches from which the anomalies derive, and they are subdivided according to whether the vessels were patent or appeared wholly or in part as fibrous cords. The derivation of these subvarieties from the primitive arches has been adequately emphasized elsewhere.[3, 4]

The reported cases of double aortic arch collected in 1936 by Blincoe, Lowance and Venable[5] numbered forty. In some cases there were completely functioning right and left aortic arches having patent lumens from beginning to end, while in others only one branch was open to the passage of blood. The majority of reports describe asymptomatic dissecting room specimens. Additional congenital defects in the heart or great vessels have been occasionally encountered but not with any uniformity or special frequency. It is of interest that all cases clinically recognized were in adults, in whom physical findings and radiologic distinctions are much clearer and more distinct than in the infant.

Within the case reports in the literature are included the infants whose histories are summarized below. These all presented a more or less similar clinical picture, consisting of stridulous breathing, chronic cough, respiratory distress while feeding, failure to thrive, susceptibility to bronchopneumonia, head retraction, and malnutrition.

SUMMARIES OF CASES IN LITERATURE

CASE 1.—C. Th. von Siebold.[6] Infant was 10 days old at death. Cyanotic and feeble since birth. Breathing was loud and stertorous and not improved by toilet of the mouth and nose. During nursing the child would drop the nipple almost every minute, crying, and the blue color of the body would increase. Stridor persisted until death. The necropsy showed congenital heart lesion with defect of interauricular septum and complete transposition of great vessels. There was also a double aortic arch forming a ring which encircled the trachea and esophagus. The ductus arteriosus was normally placed and patent. The author ascribed the dysphagia and stridor to the aortic collar and the cyanosis to the heart lesion.

CASE 2.—Buschendorff.[7] Male infant, aged 6 weeks at death. Symptoms consisted of loud stertorous breathing, with expiration and inspiration prolonged and labored. Attacks of cyanosis would appear during crying or spontaneously, and

regularly followed nursing and drinking. Birth weight was 3.25 kg. The spleen was palpable. Chvostek sign was negative. The child did poorly and died two weeks after admission to the hospital. At necropsy a normal left-sided aorta having the usual branches was present, with a large anomalous artery linking the first part of the subclavian artery with the top of the descending aorta. There was thus formed a complete arterial ring (double aortic arch) surrounding the trachea and esophagus, both being constricted at this level. The lungs were pale and the thyroid enlarged.

CASE 3.—Schleussing.[8] Male infant, aged 1 month at death. No clinical information is given except the clinical diagnosis of congenital stridor due to thymus hyperplasia. The pathologic findings included double aortic arch compressing trachea and esophagus; widely patent ductus arteriosus in normal position, right sided displacement of the descending aorta, and patent foramen ovale.

CASE 4.—Ewald.[9] White male, aged 5 months at death. Born at full term. Ever since birth the parents noted a peculiar cough and dyspnea during and immediately after nursing. Both symptoms became more marked as the baby grew older. When two months old the child was admitted to the hospital with brochopneumonia. There was considerable difficulty in breathing which was partially relieved when the head was retracted. He had many paroxysms of dyspnea with cyanosis and bitonal cough. The pneumonia cleared, recurred, and cleared again. Following x-ray treatment for thymic enlargement the respirations became less labored, but the child ate poorly and failed to gain weight. In the last two months of life stridor and dyspnea grew very noticeable, and there were several nearly fatal attacks of suffocation. Emaciation developed, and the child expired at five months.

The clinical diagnoses were stenosis of trachea and inanition. Necropsy showed a double aortic arch, of which the left branch was completely stenosed and the lumen obliterated for a short distance beyond the origin of the left subclavian artery. The lower part of the left arch was present as a blind blood-filled diverticulum arising from the junction of the right arch with the descending aorta. The ductus arteriosus was normal.

CASE 5.—Herrmann.[10] White female, aged 8 months at death. Gestation had been normal and the birth weight was 9½ pounds. Cyanosis and wheezing were present at birth, but cleared up promptly. The wheeze recurred at 6 weeks. A roentgenogram taken at the University of Nebraska Hospital at 10 weeks of age showed slight widening of the shadow of the upper mediastinum.

One radiation treatment given for possible thymic enlargement gave some relief for about six weeks, after which time the wheeze returned with accompanying cough and loss of weight. She was admitted to the hospital when 6 months old weighing only 12 pounds 14 oz. The observations were summarized as follows: an undernourished child with a chronic peculiar staccato cough, wheezing respiration, and coarse gurgling râles on inspiration. Further roentgenograms did not verify an enlargement of the thymus but described an unusual contour of the upper portion of the heart shadow. Bronchoscopic examination discovered no constriction of the trachea. While in the hospital the child contracted bronchopneumonia and gastroenteritis, from which she ultimately died. Toward the end, head retraction, cyanosis, dyspnea, and regurgitation grew progressively more severe.

The necropsy showed emaciation, aspiration bronchopneumonia, and ulcerative colitis. There was a double aortic arch encircling and constricting the trachea and esophagus. The ductus arteriosus was patent and in normal position. The left vertebral artery arose from the left aortic arch.

CASE 6.—Snelling and Erb.[11] White female, aged 5 months at death. Normal gestation. Infant weighed 6 pounds when born. Ever since birth there had been observed a constant audible inspiratory stridor with indrawing of the chest wall, which would become more pronounced during excitement, crying, and feeding. In

the nursing periods especially, the dyspnea would become much aggravated, and nursing was frequently interrupted so that the child might get her breath. A brassy dry hacking cough had been present since two months of age. Beginning at 3½ months, cyanotic collapse attacks requiring artificial respiration became more and more frequent, taking place during or following feedings. A chronic upper respiratory infection appeared. The last month of life was spent in the Hospital for Sick Children at Toronto where chest roentgenogram showed peribronchial infiltration. Barium study demonstrated both cardiospasm and a constriction of the esophagus opposite the third and fourth dorsal vertebrae. Death was due to pneumonia. The clinical diagnosis was right aortic arch. The necropsy showed a double aortic arch compressing trachea and esophagus, bronchopneumonia, otitis media, and malnutrition.

COMMENT

The case here reported (L. H.) presented the same clinical picture as did the infants whose histories are summarized above. In every instance the symptoms were mild or absent at birth, but became progressively more marked as time went on, and led to death before the age of 6 months. In none was the correct diagnosis of double aortic arch made before death, although in one infant (Case 6) the related condition of solitary right arch was suggested.

In this disorder physical examination reveals nothing unusual except perhaps alteration in the auscultatory breath sounds secondary to tracheal stenosis. Roentgenograms of the chest may show some broadening of the upper mediastinal shadow, but this sign is of little practical value since other conditions in the chest give rise to the same appearance. Confirming evidence may be found in the radiologic detection of esophageal constriction at the aortic arch level when barium is fed. Irradiation therapy over this region causes no diminution of the radiologic contours although two patients were temporarily relieved by such treatment. Direct fluoroscopy in very skillful hands may succeed in demonstrating the two arches.

If the diagnosis could be correctly arrived at during life, it is possible that surgical treatment of the arterial stricture might be attempted.

Attention has recently been called[4] to the clinical and roentgenologic findings shown by adults having a double aortic arch with complete patency of the right arch and persistence of the left in the form of the left subclavian artery, a short occluded isthmus portion, and an upward, blind diverticulum from the termination of the right arch. Arkin described six cases, two having post-mortem corroboration. None showed symptoms. Discovery of the anomaly was incidental to routine physical and radiologic examination of the chest and was based on characteristic fluoroscopic and physical findings.

The distinctive characteristic of constricting double aorta in infancy seems to be the distressing aggravation of symptoms which takes place during swallowing. Differential diagnosis must include all conditions which produce chronic respiratory tract obstruction at this age period. There is one infant on record[12] having a history almost identical with

the seven presented above, in whom the constricting vascular circle was formed by a right aortic arch, the obliterated ductus arteriosus, and the pulmonary artery.

It appears, therefore, that the presence of double aortic arch cannot be suspected during infancy unless the trachea and esophagus are mechanically interfered with, in which event the symptoms are more or less characteristic, and the prognosis becomes very poor.

SUMMARY

An instance of double aortic arch constricting trachea and esophagus is described, along with six others collected from the literature. These cases showed a common and more or less characteristic syndrome, which consisted of stridorous breathing, dysphagia, chronic cough, susceptibility to bronchopneumonia, head retraction, malnutrition, and onset during early infancy. The most distinctive symptom was an increase in respiratory distress during feeding.

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American Academy of Pediatrics

Proceedings

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 9, 1938

Panel Discussion on the Thymus Gland

Chairman: Dr. A. Graeme Mitchell, Cincinnati, Ohio
Assistants: Dr. Edith Boyd, Minneapolis, Minn.
Dr. W. Edward Chamberlain, Philadelphia, Pa.
Dr. Nathan H. Einhorn, Philadelphia, Pa.
Dr. Henry F. Helmholz, Rochester, Minn.
Dr. Alfred Howard Spohn, Vancouver, B. C., Can.

CHAIRMAN MITCHELL.—In this panel we want to arrive at some conclusions among ourselves which we can present finally and which we hope will be of some assistance to the clinician. Some questions we wish to ask pertain to the possible functions and the physiology of the thymus gland and Dr. Einhorn will certainly take part in that part of the discussion. Dr. Boyd will discuss the roentgenographic diagnosis and treatment. In my opinion, Dr. Helmholz belongs in the group of thymus skeptics, and I hear that Dr. Helmholz thinks that Dr. Spohn is a thymus enthusiast.

There are several questions, and I am going to ask some of those questions. As a beginning, "Has this particular bit of tissue called the thymus any function and if so what is the proof?" Dr. Einhorn, will you open the discussion?

DR. NATHAN H. EINHORN.—I have taken from the literature a number of the more important evidences indicating that the thymus may have an endocrine function. Briefly, the following contributions may be mentioned:

1. Experimentally its behavior resembles that of other endocrine glands. Thymus excess produced by injection of thymus extract has resulted in an acceleration in the growth and development of the offspring in successive generations of treated parent rats. This increased rate of growth is most pronounced prepubertally when the thymus is at its largest and in its most succulent state. Thymus deficiency produced by removal of the thymus causes the opposite effect; namely a retardation in the rate of growth and development of the offspring. Thymus deficiency in the pullet has been shown to lead to the production of shell-less eggs. The effects of thymus deficiency can be readily overcome by administration of thymus extract or by thymus implants. The iodine-reducing substances, glutathione, ascarlic acid, and apteine found by Dr. N. K. Shaffer to be present in thymus extract, accelerate growth and development in the offspring of normal rats but are ineffective in thymectomized rats, indicating that these substances have trophic actions.

As with the admittedly well-known endocrine glands, there seems to be an interrelationship between the thymus and other glands, as is indicated by the following evidence: At puberty the gonads undergo marked development, while the thymus undergoes marked recession.

2. Castration causes persistence and hyperplasia of the thymus.

3. Adrenalectomy causes a persistent enlargement of the thymus. Conversely, it has been observed that animals with large thymus glands have small adrenal glands.

4. Thyroidectomy results in an increase in the size of the thymus, while the administration of pituitary thyrotropic hormone results in a reduction in the size of the thymus. Hypophysectomy done prepubertally delays involution of the thymus. Irradiation of the thymus in one- to two-day-old rats results in retardation in growth and virility in the male, and finally the administration of thymus extract to normal rats produces early maturation of the ovaries and testes as well as increase in the number of eosinophilic and basophilic cells in the pituitary gland.

DR. MITCHELL.—Dr. Einhorn will show a moving picture later to bear out some of the statements he has made here. Dr. Einhorn, this work of which you speak has been done entirely on rats, has it not?

DR. EINHORN.—Yes, and much of the work that I have quoted has been the work of other investigators. My own work has, of course, been with Drs. Leonard Rowntree, Arthur Steinberg, and W. K. Shaffer.

DR. MITCHELL.—Is there any application of these experimental studies which can be translated to the clinician?

DR. EINHORN.—There are no clinical results from our work as yet. May I note that the absence of the thyroid gland produces an increase in the size of the thymus.

DR. HENRY F. HELMHOLZ.—I would like to ask Dr. Einhorn whether he has found in cases where death has occurred from toxic goiter that there is not an enlarged thymus.

DR. EINHORN.—I cannot answer this question from personal experience. This observation has, however, been recorded in the literature by Hammar.

DR. MITCHELL.—I am going to ask Dr. Boyd what constitutes a normal thymus gland.

DR. EDITH BOYD.—When we come to consider the question of normal thymus, we are faced with the fact that the thymus is one of the most sensitive organs in the body. Inanition from any cause whatsoever, inanition from lack of water alone, inanition from lack of water and food, inanition from infection, reduces the size of the thymus within three days to about one-third of its size in a well-nourished animal, including the human.

I will show some lantern slides which set up a reasonable standard of normal size of the thymus gland based upon autopsies of thymuses from individuals dying of accident within 24 hours of their injury. All other cases have been excluded.

We consider the cause of death as adequate when the child fell from a third-story window or was knocked down by an automobile and picked up dead with a fractured skull; or when we recovered 25 mg. of strychnine from his stomach, and the like.

In Fig. 1 I want to point out what we consider a normal thymus gland when we pick individuals who were in a good state of nutrition at the time of their death. Here I have normal standard set on the basis that the middle 50 percentile line represents the average, so that it is expected that half of the weights of normal thymuses will fall above this middle line, and that 50 per cent will fall between the 25 and 75 percentile lines. It is expected that 80 per cent of normal individuals will fall between the 10 and 90 percentile lines, and that 20 of the normal subjects will fall entirely outside the shaded zone. Now I have indicated the upper limit of normal weight of the thymus as ordinarily given in the literature, namely, *20 gm.* You will notice that it almost hits the lower 10 percentile on the line in children from 5 to 15 years of age, and that after about six months it is below the average weight of the thymus.

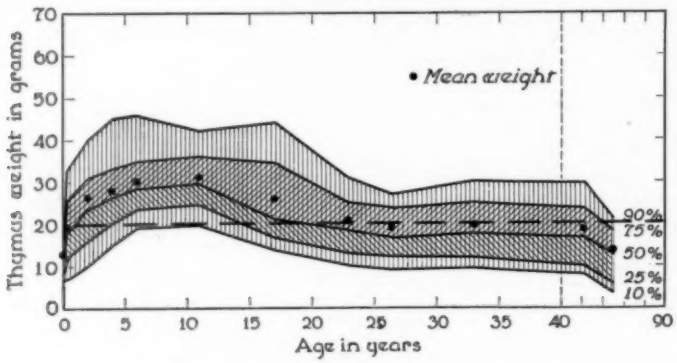

Fig. 1.

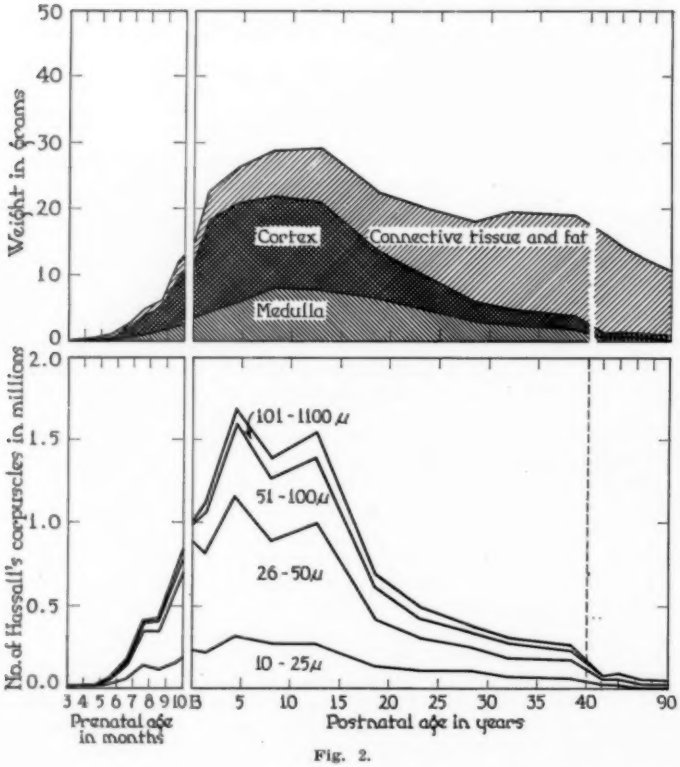

Fig. 2.

It is very hard for me to consider as abnormal any organ that is below the average size of that of well-nourished individuals; it is certainly not an enlarged gland, since it is in the lower half of the normal range.

The next slide (Fig. 2) brings up another question. The thymus is made up of three distinct tissues: a medulla which contains Hassall's corpuscles, the cortex

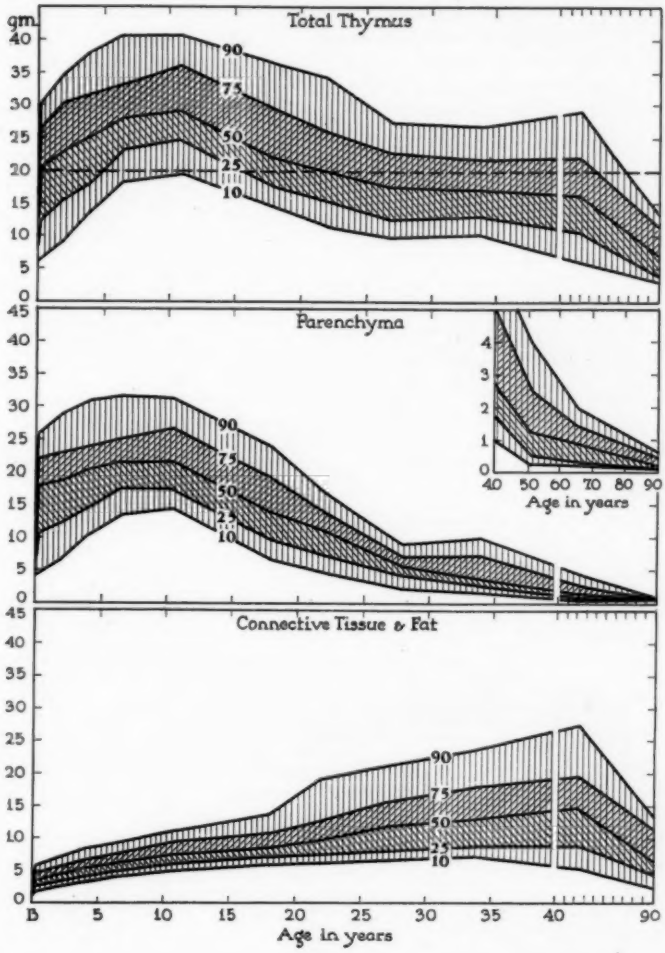

Fig. 3.

made up of framework that contains chiefly lymphocytes, and the supporting connective tissue. The slide demonstrates that the cortex constitutes the largest portion of the weight of the thymus in the early years of life. After puberty, however, the connective tissue and fat make up the greater part of the weight of the thymus, so that parenchymal tissue is decreasing. What about this parenchymal tissue? In Fig. 3 in the middle panel I show the whole parenchyma. The middle, dark shaded zone includes the middle 50 per cent, and the outer zones include the middle 80 per cent of normal parenchymal weights. Here I am entirely working from Hammar's material. These graphs of component parts are based entirely on his extensive data. I think his monumental work is not recognized primarily because his German is difficult to read. The Irish woman who translated the more difficult sections for me wrote: "When an Irishman translates into English the German written by a Swede, what you are about to receive is the best that can be expected."

Here you see the demonstration that parenchyma increases with age in the early period of four or five years and then sometime around puberty, or a little before puberty, it begins to decrease, while at the same time the connective tissue and fat continue to increase in a rather uniform manner. Now, this parenchyma is made up of two quite different tissues, the cortex and medulla. Fig. 4 shows you these separately.

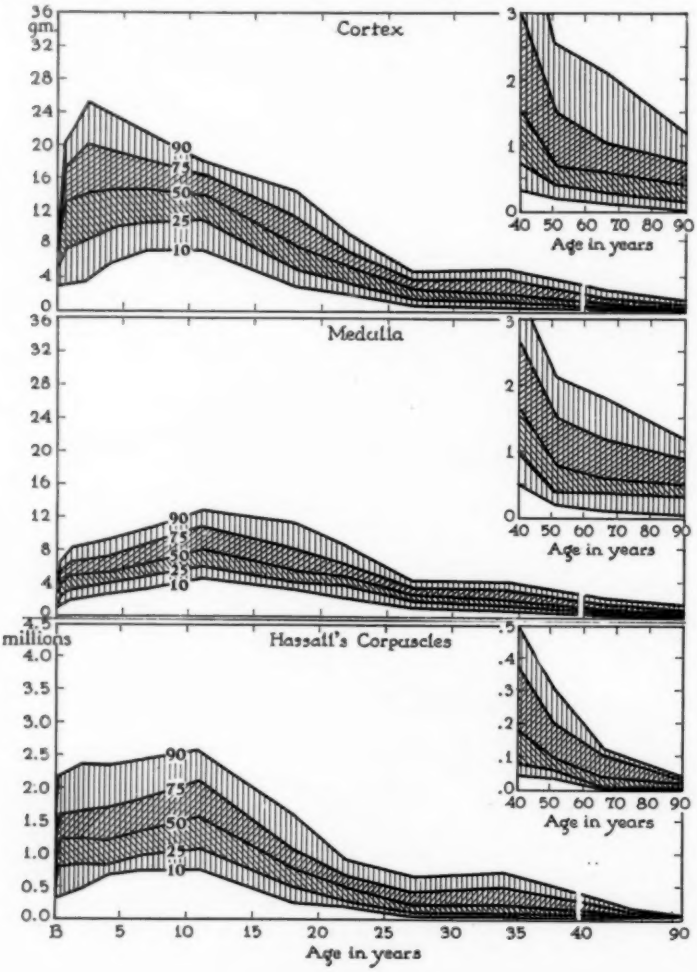

Fig. 4.

And here you see the cortex which is made up chiefly of leucocytes which migrate from the thymus during all types of inanition. You see that the growth in the cortex takes place in the first six years, then it is about stationary in weight, and then begins decreasing slightly before puberty. The medulla itself increases rapidly in the first few years, then increases slowly to sometime around the age of 12 to 13 years, and then decreases in size. As age increases there is also a decrease in

variability. This slide also shows that the corpuscles which are part of the medulla tend to parallel in their numbers the general pattern of the medulla. Now this gives a general picture of what happens to the thymus when we limit our data to those persons who have died of accident within twenty-four hours of their injury and in which there has been no question whatsoever in the mind of pathologists that death was due either to trauma or to some such cause as poisoning by strychnine or carbon monoxide.

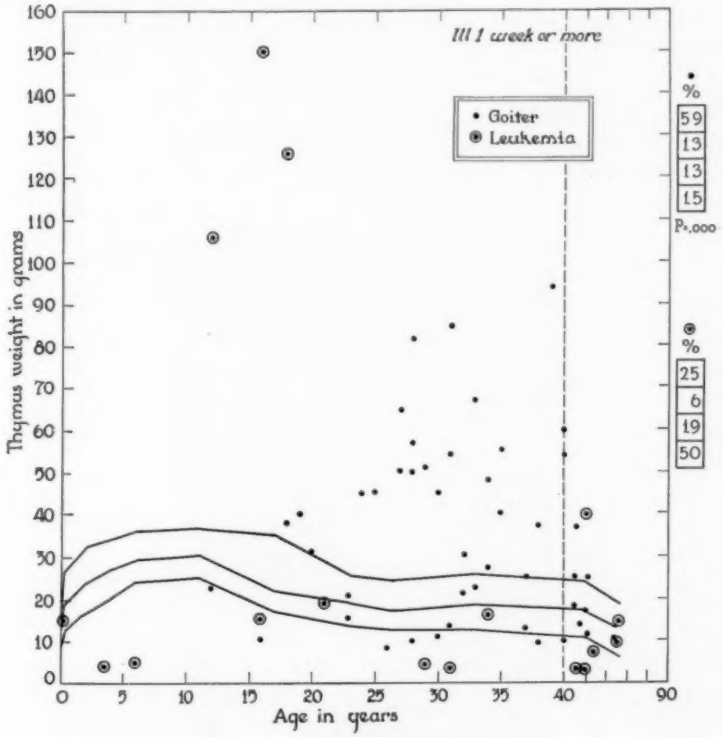

Fig. 5.

I think that gives the normal picture. Now the question has already been brought up concerning enlargement of the thymus in exophthalmic goiter, and Fig. 5 will give the evidence on this. Here you see that in exophthalmic goiter we unquestionably have enlargement of the thymus. I have rarely seen any thymus above 60 grams in weight in the case of an individual killed in an accident, and yet here you see weights ranging up well above 65 gm. So here is evidence in the human being of an enlargement of the thymus in exophthalmic goiter, and also, as Fig. 6 shows, this enlargement is due to increase in functional tissue, the parenchyma, and not due to increase in the connective tissue.

DR. MITCHELL.—What significance do you think all this has in relation to such a matter as sudden death as related to the size of the thymus?

DR. BOYD.—What has been called the enlarged thymus is the normal thymus of the well-nourished individual.

DR. MITCHELL.—Does anyone on this panel take exception to that particular statement?

DR. ALFRED HOWARD SPOHN.—Sometimes we get so-called thymic syndrome symptoms when roentgenographic shadow of the thymus is not particularly large or is within normal limits.

DR. MITCHELL.—It is a good time to ask Dr. Chamberlain, our radiologist in the panel, what he can tell us of the thymus and its enlargement. In other words, what is this business of enlargement of the thymus on the roentgenogram and what does it mean?

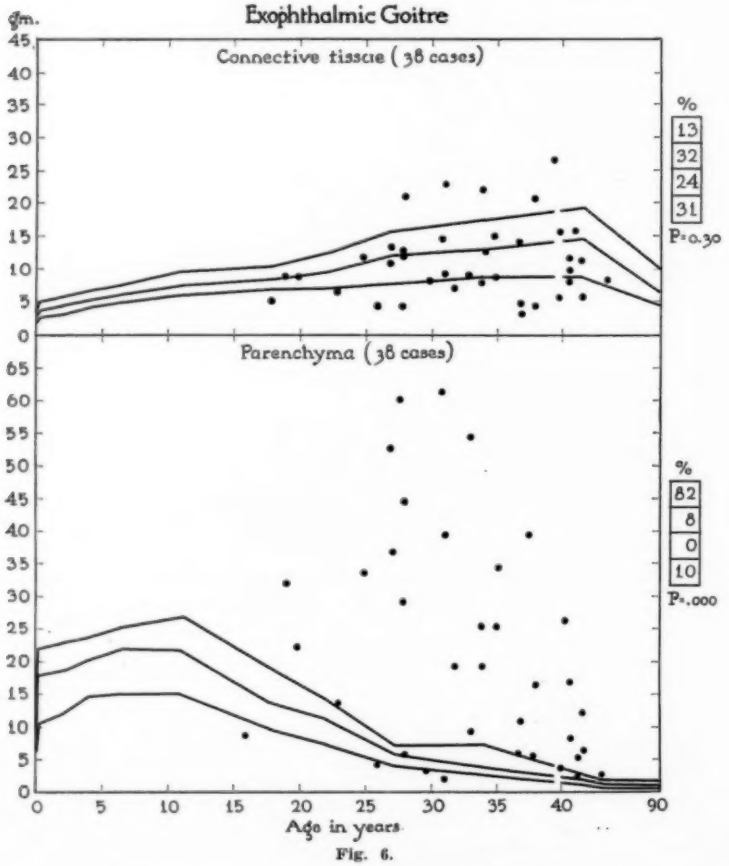

Fig. 6.

DR. W. EDWARD CHAMBERLAIN.—Radiologists have made the diagnosis "enlarged thymus" a great many times when no such enlargement was present. Some years ago this mistake was very prevalent. Neither we nor our clinical colleagues were aware of the actual limits of normal variation. Now Dr. Boyd's material shows very plainly that within the limits of normal variation the thymus gland may vary fourfold in size; in other words, the roentgenogram may reveal a thymus shadow of greater than *average* size without justifying a diagnosis of "thymic enlargement."

We do hold to this—that roentgenograms made before and after irradiation of a demonstrable thymus will show a decrease in the size of the organ as a result

of the treatment. Such demonstrations prove that the size of the thymus can be successfully visualized by roentgen examination, but they do not justify the conclusion that the thymus was abnormally large before the administration of the x-ray treatment.

A great many radiologists are beginning to doubt the significance of the thymic shadows which were formerly labeled "enlarged." But some of us continue to administer x-ray treatment to these children. We are under a considerable pressure to do so. Sometimes the pediatrician insists upon it. We know that x-ray treatment of thymic enlargement, whether fancied or real, is harmless when properly given. We know that cases of sudden death in children are likely to be ascribed to thymic enlargement and that even though the shadow we are considering may be within the normal limits, it will recede as a result of x-ray treatment. And, finally, we know that while we ourselves may be skeptical, many "otherwise competent" observers, both radiologists and pediatricians, will agree with us if we say that the thymus is enlarged. So we are but following the line of least resistance when we decide that one of these children needs irradiation.

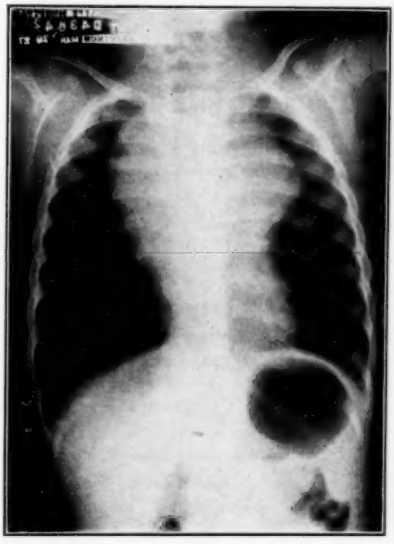

Fig. 7.

I am beginning to wonder how much of the shadow we so glibly call "thymus" is actually due to that organ. We have all of the superior mediastinal structures to cope with in this region. This morning, at the "breakfast table panel," I received a severe lesson in this matter of the anatomy of the superior mediastinum. Dr. Boyd's demonstration has shot some of my former ideas full of holes.

For example, maneuvers like the Valsalva experiment (inspiratory effort against a closed glottis while in an expiratory phase of respiration; expiratory effort against a closed glottis while in an inspiratory phase of respiration) always produce changes in the width of the superior mediastinal shadow. I have been in the habit of considering these changes as partly due to changes in the blood content of the thymus. But Dr. Boyd has convinced me that the thymus is not a very vascular organ and I realize that the great vessels must have been the chief factors in the changing shadow.

Now I think I ought to say something about the connection between thymic enlargement and respiratory embarrassment, even though I think, or at least I hope, that clinicians rather than radiologists were the ones who raised that question. I have never been able to see how the stridor that children have could possibly have anything to do with the thymus. It just is not in the cards that a large organ in that region would produce the kind of stridor that has been heard in these cases.

Fig. 7 is a roentgenogram of a patient who did have a real enlargement of the thymus due to a thymoma. These symptoms are somewhat rare, but this one was a proved case. You will notice a very large thymus shadow, and I want to tell you what the breathing of this child was like. Inspiratory as well as expiratory passage of the air was impeded. This little patient was given irradiation; before the roentgenogram showed any decrease in the size of that thymus, respiratory embarrassment was about 50 per cent improved; and by the time the slightest decrease in the size of that thymus could be measured on the roentgenogram, there was complete relief from the respiratory embarrassment. In other words, in this case the trachea was compressed, and instead of hearing the laryngeal stridor which we have so often ascribed to the thymus we had the inspiratory and expiratory stridor that I have just illustrated.

DR. MITCHELL.—Dr. Boyd, do you have anything to say here?

DR. BOYD.—I will bring up what was discussed at the breakfast table. Dr. Chamberlain asked me what was the largest vein going into the thymus gland, and I said that it was the one that goes directly into the innominate vein and measured about 2 mm. in diameter. I think the thing that is overlooked is that the thymus vein fits closely around the innominate vein. If there is congestion in the mediastinum, it is probably due to dilatation of the innominate vein, and that is probably what is seen on the roentgenogram. At least Dr. Chamberlain was enough of a gentleman to grant that that might be it. The thymus itself is not particularly vascular.

There is another point which may be applicable in some cases of relief of symptoms following irradiation. In children dying of acute respiratory infections (pneumonia) within the first few days of illness, the mucous membranes of the trachea and bronchi are frequently engorged. Unquestionably in infections there is enlargement of lymph nodes draining that infected area, and reduction of these by irradiation would cause improvement. I raise the question that, if relief is obtained from irradiation in such cases, why not say it might be due to a reduction of hypertrophy of the lymphoid tissue? In children dying of infections under 24 hours of the onset of their illness, in very rapid fulminating infections, the weight of the thymus is still within the normal zone of variation. In death from one day to one week after onset of illness we get obvious reduction in the size of the thymus. I can show this on a slide.

DR. MITCHELL.—Pardon me a moment, Dr. Boyd. If I understand you correctly, Dr. Chamberlain, you demonstrated roentgenograms here in which the patient did have symptoms with an enlarged mediastinal region and these symptoms disappeared after x-ray treatments, but before there had been a reduction in size.

DR. CHAMBERLAIN.—Before the reduction was visible on the roentgenogram but the reduction in size must have taken place.

DR. MITCHELL.—I just want Dr. Helmholz to be thinking about the next question I am going to ask him, which is whether he thinks that the thymus gland by enlargement can cause symptoms of dyspnea and cyanosis.

DR. BOYD.—Now on this particular slide (Fig. 8) I have the middle 50 per cent zone and that is the 75, 50 and 25 percentile from birth to 90 years of age in the cases of infection according to the length of time the individual lived after onset of symptoms. The data presented show that within from one to seven days

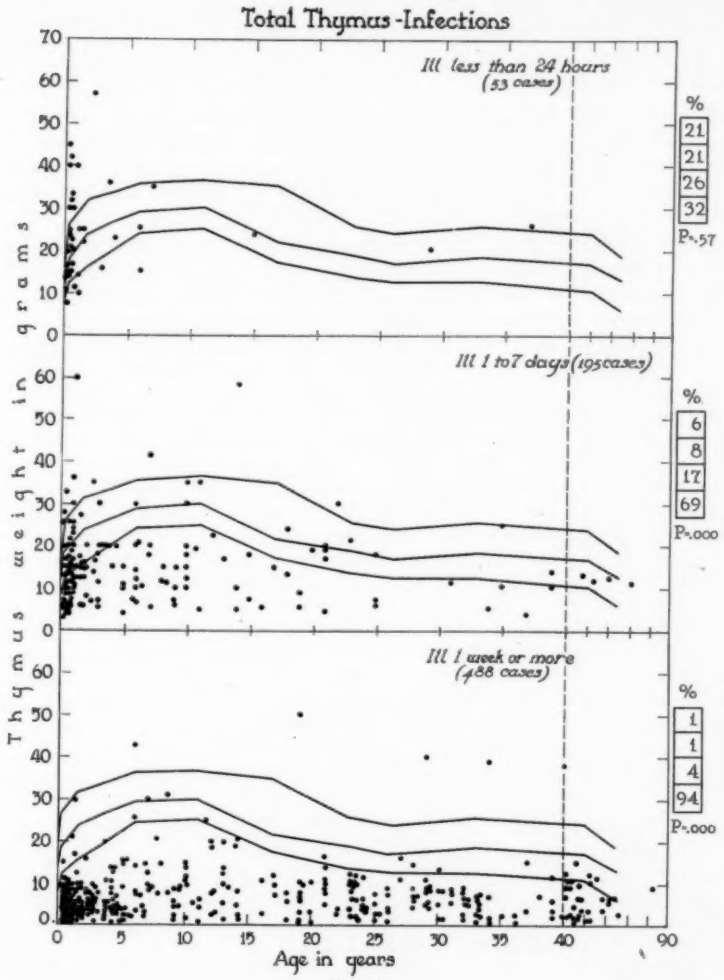

Fig. 8.

of illness there is significant reduction in thymus weight and that in infections which have lasted over one week, 94 per cent of the thymus weights fall below in the lower 25 per cent group of weights.

Now these are the thymus weights from which the standards were set up when it was stated that any organ above 20 gm. in weight was hypertrophied, and you see actually that the pathologic reduction was considered normal.

DR. MITCHELL.—I think we ought to stick for the moment to what we really started discussing, namely, whether enlargement of the thymus can cause symptoms. What Dr. Boyd has told us, I think we accept. There is no argument from the anatomical viewpoint that what in the past was considered enlargement of the thymus was the normal thymus, and I think Dr. Boyd has demonstrated that to the satisfaction of all of us. A question does arise at times because this is necropsy

material, and it is queried whether perhaps something happens after death which changes the picture. Therefore, we come back to the matter of roentgenograms. So far we have discussed the matter of roentgenograms rather briefly. The plate which you have showed us, Dr. Chamberlain, was an anteroposterior view. What does such a picture mean in relation to pressure symptoms?

DR. CHAMBERLAIN.—We must, of course, start out with recognition of the fact that the lateral lobes of the thymus can be very large without producing any difficulty, for the reason that there is plenty of space for the lateral lobes to occupy alongside the pericardium on both sides.

DR. HELMHOLZ.—On what basis, Dr. Chamberlain, do you usually give x-ray treatment in cases of thymic enlargement?

DR. CHAMBERLAIN.—I have usually been permitted to decide whether the enlargement was significant. Now when I say "significant enlargement" I must go on the defensive immediately because you may say that it is not of significance, but I think I should tell you a story because I agree that we may have a very large thymus shadow without symptoms.

Langley Porter was writing a book in 1919 and he asked me to get for him a normal roentgenogram of the chest of a 1-year-old child. I said that would be easy because my sister had a little girl who was born just a year ago, and at the age of 1 year she had never had an infection or any trouble of any sort. So I got the niece to come over and be x-rayed on her birthday. To my amazement she had a huge thymus, bigger than her heart; she had absolutely no signs of symptoms, and never had had.

I did nothing about it, I did not treat the child because I thought that would be meddlesome. I had discovered this thing accidentally, and for all I knew it was within the limits of normal variation. Three years later, however, when she was 4 yearse old, a nose and throat specialist decided to give the child an anesthetic for the purpose of seeing whether she had adenoids in her nasopharynx. When that short anesthesia (it was given for the purpose of giving her just a brief moment of unconsciousness) was administered, she immediately went into a deep cyanosis and was absolutely choked up.

DR. HELMHOLZ.—Does not this often happen when children have normal shadows?

DR. CHAMBERLAIN.—(If you will do your heckling when I finish my story) I think, Dr. Helmholz, that you are trying to take away from me my most precious theories regarding my most remarkable cases.

At any rate the point that I thought was significant was that, when the child had become absolutely limp and relaxed, she began to breathe again, and I began to question whether these so-called thymic deaths are really due to the thymus. I said to myself: "Why should room for airway be re-established when the struggles stop and the child is relaxed?" My niece is now a girl of 19 or 20 years, and we have never irradiated her thymus, not even after that episode, but we did take films once in a while. The next film was taken when she was about 12 years old, and she had a perfectly normal mediastinal shadow.

DR. HELMHOLZ.—I think you know, Dr. Chamberlain, that I just want to emphasize some of the points that you are making, because I could not have a better case to back up my story than the one you have told. Unfortunately I have had similar cases where the child at the onset of anesthesia stopped breathing and only by artificial respiration were we able to revive him. I do not believe that such an incident proves at all that the thymus is in any way responsible.

DR. BOYD.—What is the basis for standards of the normal thymus limits on the roentgenographic plate?

DR. CHAMBERLAIN.—I have no organized data. I can only say that I believe I carry in my head some data which allow me to form opinions. I believe also that

I can recognize the variations of the normal and that I know when a thymic shadow is bigger than the average or bigger than 80 per cent of the cases that I consider normal.

DR. BOYD.—What do you consider the significance of something that is bigger than average?

DR. CHAMBERLAIN.—I keep a biological distribution chart currently in front of me—for heart size, for position of the viscera, and for the size of the thymus. However, I do not become hysterical when I see variations from the average, and I give as evidence of that the case already cited in which when the thymus was bigger than the child's heart I did not even administer irradiation.

DR. MITCHELL.—Do you think an increased size of the shadow in the mediastinal region on the roentgenogram can be associated with such symptoms as dyspnea or cyanosis? Do you think that a large thymus does cause symptoms of obstruction?

DR. SPOHN.—It may or it may not cause symptoms of obstruction, but symptoms due to obstruction are in my opinion very rare.

Our chairman has suggested that before this demonstration was through we might be able to throw out the term "status thymicolymphaticus." I quite agree with him, but I would say that if we do it we must substitute something else for it such as "thyro-thymicolymphaticus." Yesterday I attended a demonstration on fluid administration at a round table conference, and I was amazed to find that they have in the East certain problems that some of us had almost forgotten about in Vancouver. I mention this to emphasize that there is a certain geography of disease and because, if certain competent observers in one part of America do not observe certain clinical conditions, this does not necessarily mean that such conditions do not exist in other parts of the continent.

I would like to limit most of my remarks to the relationship anatomically, physiologically, and pathologically between the thyroid and the thymus glands. Also I would suggest that there is some significance in the decrease in incidence of occurrence of this syndrome in certain goiter districts following the general use of iodine therapy. Now I might say that such men as Dr. Bilderback, Dr. Durand, and Dr. Barnett, and Dr. McCormack, as well as myself, went on record twelve years ago about the great frequency of this syndrome, and I do not think we were seeing things. Now we rarely see such symptoms, and I make the suggestion that, when, for example, in British Columbia we can change the make up of animals and plants, and I think of human beings, by the judicious administration of iodine, we should give more consideration to this thymus-thyroid relationship. I remember that in 1929 Prof. Feer of Zurich told me that cases of status thymicolymphaticus had decreased in Switzerland as iodine therapy became more extensive. I emphasize also the fact that so-called status thymicolymphaticus symptoms may occur when there is slight enlargement or when an enlarged shadow in the thymus region cannot be demonstrated. Individuals exhibiting this syndrome have certain physical similarity. I think also that x-ray treatment over the region of the thymus produces an alleviation of certain symptoms which are looked upon as being related to the syndrome under discussion.

DR. MITCHELL.—Would you mind mentioning the symptoms of this syndrome at this point?

DR. HOWARD SPOHN.—They are dyspnea of an intermittent type not related to cardiac disease or atelectasis; cyanotic attacks not related to cardiac pathology; intermittent suffocative spasms with or without crying or temper attacks; stridor, usually expiratory and not connected with a nutritional state such as rickets or with obstruction of the trachea from mechanical or other causes; breath-holding spasms accompanied by cyanosis and shock; shock and collapse from seemingly insufficient causes such as opening furuncles, administering anesthetics, etc.

DR. HELMHOLZ.—Dr. Spohn, do I understand you to mean that all these symptoms are due to an insufficiency of iodine?

DR. SPOHN.—No, not at all.

DR. HELMHOLZ.—Not even when you state that since the introduction of iodine these cases have practically disappeared in your goiter belt?

DR. SPOHN.—No, I do not think that is the right conclusion. I think that just because iodine relieves or changes certain conditions in the thyroid, it is quite unscientific to say that these things are produced by lack of iodine. For example, in malaria quinine is a curative agent in the treatment of this disease, and yet malaria is not caused by lack of quinine.

Another point: x-ray treatment over the thymus region produces alleviation of these symptoms, and there appears to be no scientific proof whatever that irradiation in competent hands and in recognized dosage has produced any physical or mental deterioration. Other physiologic observations also, such as those made by Dr. Einhorn, with which I am perfectly in accord, indicate that the thymus is a gland of internal secretion.

May I say this: according to Warthin, Williamson, Barry and Pierson, McCarrison and others, especially Warthin, who is familiar to you, practically every adult dying of certain types of toxic goiter showed pathologic changes in the thymus gland and an enlargement which in normal adult life is unusual. Only last week in Vancouver we saw a girl of 24 years of age with a toxic goiter who succumbed unexpectedly. She had a small hypersecretory thyroid and a large thymus. On the train I met a pathologist from Portland who had witnessed a similar occurrence.

In regard to anatomical connection: Williamson states that quite commonly a series of cysts can be followed almost in sequence from the hilum of the thyroid into the upper pole of the thymus along the so-called stalk or ligament of the thymic lobe. These varicosities often extend into the substance of the thymus in the mediastinum. The region of distribution of the lymph cysts coincides with the region of distribution of thymic tissue from the hilum downward into the mediastinum. That isolated, as well as compact, masses of lymph tissues in this region are thymic tissue is demonstrated by the finding, even in the hilum of the thyroid lobe, of the characteristic Hassall corpuscles. Careful dissection of the stalk of the thymus reveals the fact that it takes origin in the hilum of the thyroid lobe. This stalk, when it is well defined, is seen to be composed of vessels which have all the characteristics of lymphatic vessels. Lymph is encountered in the channels. Frequently the component lymphatics, with care, can be dissected from the lateral surface of the trachea, on which they lie, and traced to their origin in the hilum of the thyroid lobe. On the other hand, these vessels may not be collected together into a cord or leash, but may spread over the tracheal surface of the thyroid lobe and run down almost independently into the thymus. Thus it seems clear that there is a very definite lymph system which emerges at the hilum of the thyroid and passes directly into the lymph spaces of the thymic nodes.

There are two processes that occur in the normal thyroid gland: one is passive accumulation of colloid, or colloid storage; the other is the active process of secretion. Colloid is not secretion but is possibly of the nature of a carrier or vehicle which, like the taurocholates and glycolates of the bile, is continually in circulation in the body. Only the excess or reserve of the bile is stored in the gall bladder, and Williamson suggests that only the reserve of the colloid is stored in the thyroid gland by the process of colloid storage.

There are three physiological phases in the thymus gland: (1) a lymphocytic stage, (2) a granular lipoid stage, and (3) a vesiculated fat stage. These phases of physiologic change are similar to changes described by Gulland and Job in the so-called secondary lymphatic glands. The thymic gland, like other secondary lymphatic glands, exhibits great difference in appearance during the course of its activity. During the normal active secretory phase of the thyroid, a lymphocytic secretory phase can be demonstrated in the thymus by sections made at such times.

As will be mentioned later, a different phase is shown in the thymus in such an abnormal state as toxic goiter. In a publication Williamson demonstrates that the thymus and thyroid may in many ways be regarded as one organ and that the thymus up to puberty is engaged in detoxicating one of the thyroid secretions, namely, the secretion of hyperplasia. Also, one other point: one hears of many deductions in regard to status thymicolymphaticus that are made on observations of children from 3 to 10 years of age. Statistics have been collected of thousands of cases taken around the tonsil age. In my experience, 98 per cent of all so-called thymic syndrome deaths occur within the first eighteen months of life.

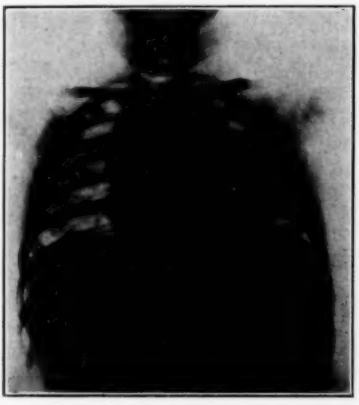

Fig. 9.

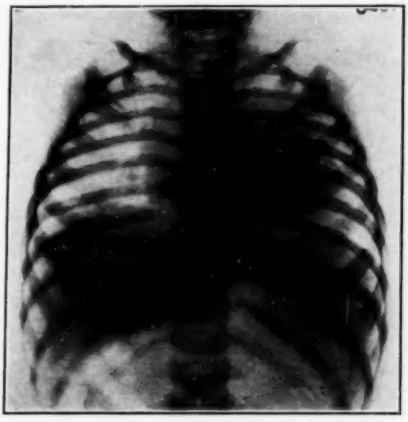

Fig. 10.

Fig. 9.—Squamous type of enlarged thymus in a female infant at the age of 9 months. This shadow could hardly be mistaken for the shadow of other structures.

Fig. 10.—Case of G. T., aged 19 months. This child showed very alarming clinical symptoms as described in text. The shadow was interpreted as being due to an enlargement of the thymus. This picture was taken before x-ray treatment. No other therapy was employed.

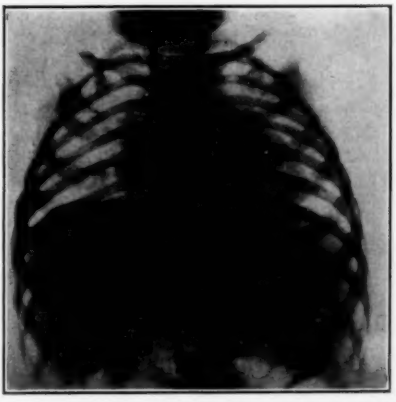

Fig. 11.—Case of G. T. Very marked thymic shadow. Patient showed alarming clinical symptoms. This picture was taken after the second x-ray treatment. Great clinical improvement was apparent at this time although the shadow is still large.

I just want to show one or two slides illustrating the type at least the West Coast pediatricians believe exhibit symptoms to which they must pay attention (Fig. 9). I know of no other therapy but x-ray for such cases.

This (Fig. 10) slide demonstrates the thymus x-ray in a child who was brought to me dying on a pillow. I am not particularly concerned about what influenced his thymus or what tissues were affected by the irradiation, but I want to emphasize the result, which was quite as spectacular as any operation in brain surgery. This second slide (Fig. 11) is after the second treatment.

DR. MITCHELL.—What symptoms did this child have, Dr. Spohn?

DR. SPOHN.—His father called me and said: "Doctor, I have a child 19 months of age who has been seen by a great number of physicians. I am losing my business through staying at home watching the child; my wife is in a highly nervous state; and if we cannot get relief, we think it would be almost better for the child to die. The child has repeated attacks, during which he becomes limp and slightly blue, and appears to be dying."

The child was brought in for examination and found to have a very marked secondary anemia. There was a history of sudden attacks in which he would become flaccid and cyanotic and yet with a peculiar characteristic pallor. He appeared to be dying. After a thorough examination he was found to have an enormous thymus. He was irradiated and had two of these attacks the following week, one attack the next week, and no further attacks. His anemia improved with dietetic measures and in two weeks he was in perfect health. Now he is a well-known football player on one of our high school teams. I do not care what you term it, whether you call it status thymicolymphaticus or something entirely different. My opinion is that I saved the child from death with x-ray therapy, and the parents were very grateful.

Now may I show some anatomical sections to illustrate some previous statements? These dissections from the Royal College of Surgeons in London have met with the approval of Sir Arthur Keith; they are from reprints of Williamson of London. It is very difficult to inject the lymphatics in these cases—very difficult indeed—and yet it is interesting to know that in 1882 Sir Ashley Cooper was able to inject the lymphatics of a calf and demonstrate the connection of the lymphatics of the thymus and the thyroid. His sections are still on view at the Royal College of Surgeons in London. The slides demonstrated the connections of the lymphatics.

DR. BOYD.—How old a person is that section from?

DR. SPOHN.—These are nearly all taken from young adults. May I point this out: Williamson has shown that, when a patient has died of toxic goiter, with symptoms which in my opinion resemble very closely the symptoms of death in the thymic syndrome seen in childhood, there is a hypersecretory stage and an absence of colloid in the thyroid. Therefore, we examine the thymus of that individual expecting it to show that it is in the lymphocytic secretory stage. But this is not the case. What we find is a peculiar *granular* stage in the thymus. One could deduce from this that during that peculiar toxic condition the secretion, which we know is present, must find its way into the blood stream and must produce toxic symptoms. Some continental workers suggest that Graves' disease should be called toxic status thymicolymphaticus.

There are in the Royal College Museum in London thirteen cases of carcinoma of the thyroid gland. Nine of them show secondary changes only in the thymus, not in the lymphatics of the neck. Therefore, I think there is here some pathologic evidence of a connection between the thymus and the thyroid.

DR. HELMHOLZ.—With regard to the findings of the carcinoma of the thyroid, we have observed seven patients now with that disease, and they have all metastases in the glands of the neck.

DR. SPOHN.—That does not alter the fact that in other cases metastases occurred in the thymus.

DR. MITCHELL.—If I understand your belief, Dr. Spohn, it is that there is a relation between the thyroid and the thymus, but I did not quite understand what that relationship has to do with the symptoms of obstruction, dyspnea, and cyanosis.

I mean, do you believe that the thymus causes these symptoms by its enlargement? Or do you think that some of these symptoms come about because of alteration of its internal secretion?

DR. SPOHN.—I think it is a matter of internal secretion.

At the beginning of this discussion your chairman described me as a thymus enthusiast. I am not quite sure just what that implies, but in order to clarify my views, might I state my present beliefs?

1. Status thymicolymphaticus is more prevalent in goiter districts. It is, however, less frequent in such districts since the more general use of iodine for endemic goiter.

2. Status thymicolymphaticus is a real clinical entity which is much more frequently observed in children under 18 months of age; and statistics concerning tonsillectomy and other operations at the ages of 3 to 10 years include an age period during which so-called thymic symptoms have always been rare.

3. This condition implies a lowered threshold of resistance against physical shock, infections, foreign protein ingestion, etc. Deaths due to so-called status thymicolymphaticus are due in the large majority of cases to an apparent toxic metabolic disturbance which resembles the deaths occurring in exophthalmic goiter of adults.

4. There are anatomical, physiologic relationships between the thyroid and the thymus gland.

5. Death from pressure of an enlarged thymus or of other vital structures is an extremely rare occurrence.

6. Prophylactic maternal ingestion of thyroid and iodine is necessary in all goitrous regions.

7. X-ray diagnosis of an enlarged thymus is only an indication of the possibility of the existence of status thymicolymphaticus.

8. An enlarged thymus is often a normal physiologic occurrence and may therefore give no clinical symptoms.

9. X-ray or radium treatment usually relieves the clinical symptoms of so-called status thymicolymphaticus and should be used conservatively until a better therapeutic measure is available.

10. There appears to be practically no scientific evidence that the use of x-rays by a competent radiologist, and with the doses ordinarily employed, has ever produced either physical or mental deterioration.

11. The status thymicolymphaticus syndrome is not a dead issue and requires further study to enable the profession to explain satisfactorily these peculiar sudden deaths to the public and themselves.

DR. BOYD.—What is the evidence for internal secretion from the thymus?

DR. EINHORN.—There is no experimental evidence available that would prove that the thymus has an endocrine secretion. This can only be inferred from some of the evidence available today. I have already presented material which makes one strongly suspect that the thymus may possibly have an endocrine secretion. This is suggested by its relationship to other glands as well as by its biologic activity following injection or implantation.

DR. MITCHELL.—However, Dr. Einhorn, the material which you presented and which you and Dr. Rowntree have published, while suggesting an internal secretion, has nothing to do with the matter of dyspnea, cyanosis, or sudden death. In other words these animals do not die, they do quite the opposite; they want to live apparently because they develop early both somatically and sexually.

DR. SPOHN.—I think these individuals die with a derangement in internal secretion as in toxic goiter.

DR. BOYD.—Have you any evidence, Dr. Einhorn, that the same thing cannot happen from extracts of lymphoid tissues or tissues other than the thymus?

DR. EINHORN.—Extracts of various glands and tissues, such as liver, spleen, lymph gland, and tonsil, have been prepared in a manner identical to that used in the

preparation of thymus extract; no critical evidence of any effect on either growth or development has been noted from the injection of any of these extracts.

DR. BOYD.—I think that is a very significant and critical experiment. If it can be demonstrated that the extracts of lymphoid tissue have no effect and extracts of thymus do, there is offered critical evidence that the thymus does have some secretion other than lymphoid tissue itself.

DR. MITCHELL.—I want to know the opinion of each member of this panel on the matter of enlargement of the thymus gland as a cause of symptoms of obstruction, dyspnea, and cyanosis. I am going to ask, beginning with Dr. Chamberlain, whether each one believes that enlargement of the thymus can cause an obstruction which will lead to dyspnea. Answer that one, Dr. Chamberlain. Is it true or false?

DR. CHAMBERLAIN.—Well, perhaps it is significant that I have, right here in this room, Mr. Chairman, friends who have referred patients to me and have either insisted upon or permitted x-ray therapy to be administered to the patient after the diagnosis of enlargement of the thymus was made, and I am very much on the spot.

However, I shall certainly be truthful, but I am not going to be very dogmatic. I can say this. I have shown you an instance in which there was a very large thymus (Fig. 7). It was a thymoma, it is true, and not enlargement of the thymus in the ordinary benign sense. In this case, as I said, we found symptoms such as shortness of breath, both ingress and egress of the air being interfered with. Now, I cannot go against certain friends of mine, clinicians, who insist that the stridor that they noted was improved after irradiation. It certainly should be significant that when I had shown that there was an enlarged thymus shadow (and I had employed a special technique in the lateral projection to show compression), irradiation of the thymus not only caused the shadow to disappear or become smaller, but that the clinician stated that the child was taking food better, breathing better, and that the stridor had disappeared.

On the other hand, there are some very interesting anatomical points that have not been emphasized as yet. It is found that in some cases certain parts of the thymus are up in the apices of the thorax, where the jugular veins and the great vessels are situated. At a certain phase of respiration, particularly with the inspiratory effort against a closed glottis such as the baby exhibits at the end of a cry, there is no question that these structures can become well jammed up. This may be of some significance. I think certainly that everything I have just mentioned could happen in a patient whose thymus was within the limits of normal size.

DR. MITCHELL.—In other words you do think that occasionally the thymus causes these obstructive symptoms.

DR. CHAMBERLAIN.—I do.

DR. MITCHELL.—You do not think that happens very often?

DR. CHAMBERLAIN.—No.

DR. MITCHELL.—But it does happen?

DR. CHAMBERLAIN.—I think so.

DR. MITCHELL.—Dr. Helmholz, will you answer that question?

DR. HELMHOLZ.—In view of the fact that Chevalier Jackson has demonstrated by examination of the larynx and trachea that narrowing of the trachea can occur from pressure exerted by a thymus, we must assume that this can happen. The only question is how often does it occur? I have been in practice for some thirty years, and I have yet to administer irradiation to a patient therapeutically or preoperatively for so-called thymic enlargement for any reason other than a new growth of the thymus. I do not mean that thymic enlargement, as we are considering it today, does not occur, but from my experience both in Chicago and in Minnesota

(both of these places are in the goiter belt) I feel that obstruction caused by thymic enlargement other than that owing to a new growth is extremely rare. I have not seen a single case in which the inspiratory and expiratory stridors, as pointed out by Dr. Chamberlain, were owing to an enlarged thymus. I have seen eight cases in which sudden death was caused by, or was associated with, the production of anesthesia.

With regard to obstructive symptoms: in many instances patients who have received irradiation because of a so-called enlarged thymus are being treated by irradiation unnecessarily and without any beneficial results. The great problem, I think, is the relationship of the thymus to the administration of anesthetics. From 1921 to 1938 at the Mayo Clinic, 4,214 tonsillectomies were performed. During and immediately after operation there was exactly one death, and that occurred in a severe case of acrodynia. The patient's condition was becoming worse very rapidly and in view of the excellent results of tonsillectomy in cases of acrodynia reported by Rodda, it was considered advisable to attempt tonsillectomy. The patient died within a few minutes after administration of the anesthetic was started.

In none of these cases I have mentioned was the thymus subjected to irradiation therapeutically, although there were many cases in which the roentgenographic shadow of the thymus appeared to be larger than the usual so-called normal shadow. I might say, however, that every one of these patients was carefully examined the day before operation. Roentgenologic examination of the thorax was performed, and, examinations of the blood and urine were made. Operation was not performed on any patient who had an elevated temperature.

There were many patients who had a severe reaction following operation, but not a single death occurred with the exception of the one mentioned. I might say that from 1921 to 1928 there were 525 patients less than five years old whose tonsils were removed.

So-called thymic death is supposed to be most frequent during the first eighteen months of life. I have the records of 1,110 patients who were operated on for harelip and cleft palate during that period, and, of these, 11 died. Two died of congenital heart disease, and in these two instances the operation was done at the request of the parents but against our advice. Three died of infection one to fourteen days after operation; two died during operation; and four died three and a half to ten hours after operation. Six of these were in a sense instances of sudden death, but, as far as we could determine, none of these patients had evidence of thymic enlargement which could cause death.

DR. MITCHELL.—Dr. Boyd, would you answer this question? Do you think that enlargement of the thymus gland can cause symptoms of obstruction?

DR. BOYD.—I think that an enlarged thymus itself, when it's truly enlarged, can unquestionably cause obstructive symptoms, such as in the case of thymoma which Dr. Chamberlain illustrated. However, the occurrence of the truly enlarged thymus is so rare that it is not something to be looked for in the ordinary healthy child.

DR. MITCHELL.—Dr. Spohn?

DR. SPOHN.—I think that the so-called obstruction from enlargement of the thymus is rare but may happen. If I may answer Dr. Helmholz, who interjected the remark concerning goiter belts: there are goiter belts and goiter belts. It has been pointed out that there are large areas in India in which there is no iodine or salt in the water but in which the water is boiled and in these districts there is no endemic goiter. When I am speaking of a goiter belt I am speaking of a belt with marked clinical manifestations such as we have in British Columbia, Washington, and Oregon.

DR. MITCHELL.—May I ask again what is the relationship of this to the symptoms that may be produced by the thymus?

DR. SPOHN.—I shall answer it this way. Formerly we had a large number of cases presenting symptoms apparently due to thymic disturbance and now we rarely see them. I am just suggesting that there may be a relationship between iodine therapy in goiter regions and a decreased incidence in status thymicolymphaticus. In certain districts where we have had somewhat similar deaths and other manifestations occurring in calves, colts, and other animals, these peculiar occurrences have practically ceased since iodine administration.

DR. MITCHELL.—That is, it is your belief that the administration of iodine had something to do with the goiter in these animals and in the human. But we are trying to get the relationship between goiter and the thymus. Do you mean, Dr. Spohn, that, as iodine was given, the goiter disappeared and the symptoms which could be attributed to the thymus disappeared also. Is that right?

DR. SPOHN.—Yes, entirely. Routine iodine therapy in goiter regions appears to have greatly diminished the incidence of dangerous so-called thymic symptoms.

DR. MITCHELL.—Dr. Einhorn, what have you to say?

DR. EINHORN.—I can only repeat what some of the others who have preceded me have said. Although true enlargement of the thymus is possible, I have not seen serious obstructive symptoms produced by such a condition. The symptoms, dyspnea, cyanosis, and stridor, are not specific of thymus enlargement; they are more often found in a large group of well-recognized clinical conditions. To illustrate my point, I have seen a 6-month-old infant who received six therapeutic irradiations for an enlarged shadow in the upper mediastinum associated with dyspnea, cyanosis, and stridor.

This child did not improve after the sixth treatment even though a follow-up roentgenogram showed complete disappearance of the superior mediastinal shadow. A closer examination of that child by means of a bronchoscope showed that it had congenital defects in the laryngeal cartilages. It is my feeling that these obstructive symptoms too often are attributed erroneously to enlargement of the thymus.

DR. MITCHELL.—A very important point that we all must stress has just been mentioned. The symptoms we are discussing, such as dyspnea and cyanosis, and even sudden death, are certainly nonspecific symptoms. They can be caused by a number of conditions, and we all realize that one has to be very careful before he attributes these symptoms to thymus.

There is a question which we had on our original list. Can any harm come about from the usual dosage of radiologic treatment to the thymus gland? I have heard it stated that idiocy follows such treatment. Do you believe that, Dr. Chamberlain? Answer yes or no.

DR. CHAMBERLAIN.—No. It is worth a trip across the continent to get a chance to help lay that ghost. When my very good friend Leonard Rowntree suggested that idiocy could result from such irradiation, he was jumped on very severely by me and others. That is one thing that does not happen, I am sure that we can say that no matter how unnecessary and superfluous irradiation of the thymus may be, and certainly we have to admit that it may be such, we have not harmed the individual with the type of irradiation that is administered by a modern radiologist for this condition.

I have case histories of three babies in which actual damage was done by irradiation for presumed enlargement of the thymus, but in every case the treatment was improperly given, and even the original diagnosis was wrong. In one case slight kinking of the trachea and a mediastinal shadow which was entirely within normal limits were mistaken for an enlarged thymus, perhaps because the film was taken in an expiratory phase of respiration when the bizarre appearance produced is hard to interpret. Irradiation therapy was administered, and then, because the x-ray appearance did not change (and it did not change because there was no enlargement of the

thymus there to begin with), therapy was continued until the child received twenty-six treatments. In another case seventeen treatments were administered, and in still another, twenty-three treatments. Two of these patients died of aplastic anemia, and the other had aplastic anemia but is still alive. These children were all grievously overtreated.

I want to ask this question. What happens when the stridor is improved after irradiation of the thymus? I will ask you that, Mr. Chairman.

DR. BOYD.—I think the question arises whether the benefit from irradiation is not due to its effects on structures in the mediastinum other than the thymus.

DR. MITCHELL.—Now we must try to get some answer to this important question of sudden death as related to the thymus.

From time to time one hears a story like this—it was perhaps the stimulation for this panel discussion: In a certain community a child had died suddenly. One physician had not ordered an x-ray of the child's thymus and suggested irradiation treatment of it. It was stated that, if this had been done, the child would not have died. That became a matter of legal testimony and record. It would be helpful if we were able to throw some light on this question. Is it true, or is it not true—or do we not know?

Of course, that brings up the matter of the term which Dr. Boyd says we cannot use, "status thymicolymphaticus." She will tell you why we cannot use such a term when she attempts to answer this question. Now I should like to ask Dr. Chamberlain a question. Would the mere fact that the thymus was irradiated have anything to do with preventing sudden death even if it could be assumed that sudden death has anything to do with the thymus?

DR. CHAMBERLAIN.—I hope, Dr. Mitchell, that my slight and wavering defense of the practice of occasionally irradiating the thymus does not indicate that I am a believer in the theory that sudden death can be due to enlargement of the thymus. Personally I think the thymus has nothing to do with sudden death.

DR. MITCHELL.—I think we all agree that, simply because the cause of sudden death cannot be found, there is no particular reason for believing that it may be due to the thymus.

DR. HELMHOLZ.—With regard to this matter: it seems to me that we must rule out all of the possible causes that might, during an operative procedure or during the course of an illness, give rise to sudden death. In many of these cases we are not able to put our finger on the actual cause of death. We are doing actual harm in hiding behind the diagnosis of status thymicolymphaticus as the cause of sudden death.

DR. MITCHELL.—Dr. Boyd, do you think that the thymus, either by enlargement or by any alteration of its internal secretion could ever cause sudden death?

DR. BOYD.—I have no record which indicates it does. We have performed a good many autopsies in cases of sudden death at the request of physicians. In a good many of them we find definite evidence of infection. My impression is that these deaths in children occur more frequently during grippe epidemics. The situation varies. Some of the children had had a slight cold and seemed to be recovering but were suddenly found dead; some had had slight symptoms of chest infection but not enough to appear serious, but then died unexpectedly; some had been obviously severely ill and died within twenty-four hours of the onset of symptoms. The thymus glands of those children who died quickly were within the limits of normal variation. The organism that we found oftenest in carefully selected areas from the lungs was the streptococcus. In some cases meningitis was discovered, occasionally only when we used Gram stains of sections of the meninges and located streptococci there.

My own impression, which only is an impression, is that probably many of these deaths were really due to the filtrable viruses and that the secondary invaders, the streptococci, were just beginning to appear.

DR. MITCHELL.—Dr. Spohn, what is your answer to this question of sudden death?

DR. SPOHN.—I think that, if thyrotoxicosis can cause sudden death, so can peculiar disturbances of lymphatic and other secretory gland organs as the thymus also lead to sudden death.

DR. MITCHELL.—Dr. Einhorn, I think you ought not only answer this question, if you wish to, but if you think that sudden death is related to the thymus you should state what you believe its relation is to an internal secretion.

DR. EINHORN.—Selye, working in Collip's laboratory, has pointed out by means of an interesting phenomenon which he designates the "alarm reaction," a thymus-adrenal relationship. In adrenalectomized animals, death follows surgical shock, exposure to colds or subcutaneous injection of formaldehyde, even though the thymus attempts to compensate by enlargement. This is an extremely important point. In adrenalectomized animals, shock produces death. In thymectomized animals the same stimuli are followed by adrenal compensation and survival of the animal. In other words, where the thymus gland has been removed and the adrenal left intact the animals survive severe shock. Selye describes this alarm reaction symptomatically, and this description bears a close resemblance to the symptoms observed in so-called status thymicolymphaticus. This work attempts to explain this condition on the basis of adrenal insufficiency.

In cases of sudden death where, after a complete and thorough search, the cause cannot be found, it seems that adrenal insufficiency offers a better explanation than does status thymicolymphaticus. Heretofore, this term has been used as a blind for a lack of knowledge, and it is time that we drop it.

DR. MITCHELL.—If there is such a relationship as has been described here, is there treatment of the thymus that would obviate this sudden death?

DR. EINHORN.—No.

DR. MITCHELL.—There is one question which I am going to ask Dr. Boyd to answer briefly. Please define status thymicolymphaticus according to its original description. In the main the term has been very badly mistreated, according to Paltauf's initial definition.

DR. BOYD.—I am sorry I have not reread Paltauf's description recently. As I remember, he described a pale, rachitic infant with prominent lymphoid tissue and a narrowed aorta. The narrowed aorta has more or less dropped out of the picture. I have never found a narrowed aorta. The thymus glands in this condition as described by Paltauf were within the ordinary range of those of well-nourished infants.

DR. MITCHELL.—There is one more question which has been passed up from the audience. Please explain the condition in a child who has convulsive seizures, a large thymic shadow and who, after x-ray treatment, has no more convulsions.

DR. CHAMBERLAIN.—There is no question but that occasionally convulsive seizures become less frequent after almost anything you do. Sometimes, however, improvement may be due to release of back pressure on the veins of the neck. I think we have seen engorgement of these veins in conditions other than an enlarged thymus. It is possible, also, that occasionally the seizures of idiopathic epilepsy are increased in frequency by congestion of the veins of the head and neck. Such congestion might possibly be caused by an enlarged thymus and relieved by its shrinkage. It would be very dangerous to attempt any scientific explanation. In some cases there is a reduction in the number of convulsive seizures after irradiation

of the thymus; in others frequency has been apparently increased after irradiation. If we irradiate properly, we can say that we have not done any harm. The competent radiologist can treat the child and also by doing this treat the anxious parents, who think something is being done. The pediatrician is helped, too.

DR. MITCHELL.—You take the pediatrician very seriously, I think. "Convulsions" is a symptom of so many things that a combination of a questionably enlarged thymus shadow and convulsions is not a very significant one.

Now I have no delusions that I can summarize this discussion to your satisfaction. It is a very difficult situation we have attempted to solve, and there are many questions that we have not had time to dilate upon. It appears to be the opinion of this panel that it is proper to say that the thymus gland occasionally causes symptoms of compression. Other causes for compression symptoms must be searched for before the thymus is incriminated. It appears also that this panel admitted that it is possible that certain enlargements of the mediastinal structures can cause symptoms of compression and that radiologic treatment has some effect on those symptoms. This, however, is not merely uncommon but rare. Does anyone disagree with the fact that, regardless of the roentgenograms, the thymus may occasionally cause symptoms of obstruction? It seems to me that that is what this panel admitted.

DR. BOYD.—I want to say—very occasionally.

DR. MITCHELL.—Extremely occasionally. I have no right to attempt to summarize what we said in this panel about convulsions—we didn't discuss it sufficiently. I may state my own belief that there is no proved association of convulsions and thymus.

Most of the members of this panel feel that perhaps it may be just as well to discard the term "status thymicolymphaticus." We are sure also that, even if the thymus is in any way related to sudden death, it could only be in a secondary capacity; there is no treatment of this organ by injection of any extract of it, by radiologic treatment, or by extirpation of it, which would have any effect upon preventing sudden death. Is there any disagreement with that?

DR. SPOHN.—I do not agree entirely. There have been some clinical cases mentioned this morning where patients in extremely critical state, and exhibiting so-called thymicolymphatic symptoms, have apparently been restored by x-ray treatment over the thymic area. No other treatment was of any avail in these cases. Part of my efforts this morning have been to admonish against a too unceremonious or precipitous burial of the status thymicolymphaticus syndrome. Burial is not a sufficient answer to such a vexing and unsatisfactorily explained condition. If it is to be locked behind medical doors, it may, like the ghost in Hamlet, appear on most inopportune occasions to torment our medical consciences.

DR. MITCHELL.—There has been an opinion expressed also by Dr. Spohn that there is some type of relationship between the thyroid gland and the thymus. Just exactly what that means to the clinician today is not particularly clear, nor does it lead to any specific idea of treatment; that is, unless what Dr. Spohn has said suggests the administration of iodine, which, acting on the thyroid, would have a secondary effect on the thymus.

I think it can be assumed that whatever knowledge we have gained experimentally concerning the functions of the thymus is not applicable in clinical medicine today.

We have agreed that great caution is necessary before stating that the roentgenogram shows thymus enlargement. Lateral plates are perhaps better than anteroposterier ones. There certainly is no relation between the size of the thymus gland and sudden death.

I do not believe that I have any right to attempt any other type of summary of the opinions of this panel.

A. GRAEME MITCHELL, M.D.

Academy News

Region I will hold its annual meeting on June 1, 2, 3, 1939, at the Waldorf-Astoria Hotel, in New York City.

Region IV has planned to have its next meeting on April 27, 28, 29, 1939, in Oakland, Calif.

There will be no annual meeting in 1939 of Regions II and III. There will be a meeting of the regional chairmen and state chairmen of Region II in St. Louis in May.

Extra copies of the pamphlet, *The Health Supervision Program Your Child Should Have*, which was recently sent out by the Academy, may be obtained from the secretary's office, 636 Church Street, Evanston, Ill. The only charge will be for express.

On April 3, 4, and 5, 1939, graduate courses in pediatrics for physicians were held in Detroit by the Michigan members of the Academy. Over thirty practical topics were discussed in the three days. The conference closed with a dinner at which Dr. Sidney Farber of Boston spoke on "The Pathology of Sudden Death in Infancy." The program was arranged by a committee consisting of Dr. Cooley, Dr. Levy, Dr. Martmer, and Dr. Johnston.

Dr. Harry C. Berger, of Kansas City, died March 5, 1939, of coronary occlusion.

News and Notes

The **Society for Pediatric Research** will hold its annual meeting on April 26 and 27, 1939, at Skytop Lodge, Skytop, Pa.

The **American Pediatric Society** will hold its 51st annual meeting on April 27, 28, 29, 1939, at Skytop Lodge, Skytop, Pa. This meeting will follow immediately the one of the Society for Pediatric Research.

Errata

In the obituary notice of Dr. Lucy Porter Sutton, which appeared on page 275 of the February issue of the JOURNAL, the following correction should be noted:

"Dr. Sutton was an assistant professor of pediatrics in New York University College of Medicine for seven or eight years. She was Chief of the Cardiac Clinic of the Children's Medical Service of Bellevue Hospital. Her work in rheumatic fever, heart disease, and chorea was noteworthy."

In the article, "A Midsummer Respiratory Infection in an Aseptically Conducted Adoption Nursery," by L. W. Sauer, M.D., and J. J. McDonald, which appeared in the March issue of the JOURNAL, the following corrections should be noted:

On page 305, lines 7 and 8, the names "Curtis" and "Chauncey" should be interchanged, making the two lines read as follows: "Five, six and seven days after Rita's admission, Chauncey in the same room, Lindley, George, and Curtis in the adjoining room, all in . . ."

Books Reviews

Medicine in Modern Society. DAVID RIESMAN, M.D., Princeton, N. J., 1939, Princeton University Press, pp. 226. Price $2.50.

In these times when medical writing for the laity consists chiefly of polemic novels, medical autobiographies of more or less interesting and unimportant lives which offer an outlet to the ego, and that excrescence on medical literature known generally as the newspaper "health column," produced by columnists, some of whom have never practiced medicine, the value of which the reviewer feels lies in the remuneration to the writer rather than in the information set forth to the public, it is a pleasure to run across a book like this. Dr. Riesman, for many years one of the leading physicians and internists in Philadelphia and a teacher at the University of Pennsylvania, has produced for the laity a book on medicine and its problems which presents briefly the past and, in more detail, the present, and which for the knowledge it contains and the breadth of view from which it is written would be hard to duplicate. Throughout, one has the vision of a wise and tolerant man who is in love with his profession and to whom medicine is an ideal.

The book is based on a series of lectures known as the Vanuxem Lectures delivered by the author before a lay audience at Princeton University. The theme lies in the author's belief that "the history of medicine is in reality an epitome of the history of civilization and should form a part of every man's culture." After a few brief chapters on the art and science of medicine and medical progress through the centuries, certain specific topics are discussed among which are cancer, medical education, medical ethics, cults, superstitions and the "family doctor." In a chapter on the social outlook in medicine, present-day problems and conditions which are the subject of so much controversy are presented. It is in this chapter perhaps that the tolerance and maturity of the author are best seen. The writing throughout is clear and simple, as good writing should be. It is a readable book that the physician may well recommend to his lay friends who are interested in the story of medicine and in its future.

Biographies of Child Development. ARNOLD GESELL, B. M. CASTNER, HELEN THOMPSON, and C. A. AMATRUDA. New York, 1939, Paul B. Hoeber, pp. 328. Price $3.75.

This is one of the most interesting books that has appeared from the Yale Clinic of Child Development. In contrast to some of the earlier publications, it has more to do with results than methods and for this reason appeals more to the average reader. In Part I the report of a series of 30 cases published ten years ago and restudied after this interval is given. The development in later childhood in nearly all instances has justified the implication of the early growth pattern. There is just enough discrepancy and failure in the prediction and outcome to impress the reader with the view that the early growth pattern does give a distinct clue to the development in later childhood. It is not too perfect to be true. In Part II a number of developmental biographies are presented from the standpoint of factors influencing the growth pattern. Thus cases of immaturity and premature birth, language and reading disabilities, and physical complications are recorded. The value of Dr. Gesell's work and methods will undoubtedly find a permanent place in the study of child development.